Learning Disabilities

New Research

Soren V. Randall
Editor

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LEARNING DISABILITIES: NEW RESEARCH

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PREFACE

A learning disability (LD) is a neurological disorder that affects the brain's ability to receive, process, store and respond to information. The term learning disability is used to describe the seeming unexplained difficulty a person of at least average intelligence has in acquiring basic academic skills. These skills are essential for success at school and work and for coping with life in general. LD is not a single disorder. It is a term that refers to a group of disorders. LD is a disorder that affects people's ability to either interpret what they see and hear to link information from different parts of the brain. These limitations can show up in many ways: as specific difficulties with spoken and written language, coordination, self control or attention. Typical learning difficulties include dyslexia, dyscalculia and dysgraphia, often complicated by associated disorders such as attention deficit/hyperactivity disorder. This new book brings together leading research in the field.

Chapter 1 focuses on numerous reviews that have appeared in the literature of learning disabilities over the past 100 years, in which Hynd & Willis (1988) concluded that by 1905 the number of observations that had emerged from the evolving literature was such that a number of tentative conclusions could be offered. Overall, the literature by 1905 supported the following: (I) reading disability (congenital word blindness) could manifest in children with normal ability, (2) males seemed to be more often affected than females, (3) children presented with varied symptoms, but all suffered a core deficit in reading acquisition, (4) normal or even extended classroom instruction did not significantly improve reading ability, (5) some reading problems seemed to be transmitted genetically, and (6) the core symptoms seemed similar to those seen in adults with left temporo-parietal lesions.

Although the prevalence of mathematical disabilities seems as high as the prevalence of reading disabilities, research interest for mathematical disabilities was very limited until now (Mazzocco and Myers, 2003; WHO, 1992). Moreover, many theoretical as well as pragmatic issues concerning mathematical disabilities still are unclear. A fundamental stumbling block is the discussion on defining a mathematical disability, or even a learning disability in general. A general search in the literature and practice shows a proliferation in the terminology used. Several authors used different terms for a deficit in mathematical problem solving, such as dyscalculia, acalculia, mathematical disabilities, mathematics learning difficulties, mathematics learning problems, mathematics learning disorders, mathematics learning disabilitiy, mathematics learning retardation, mathematics learning deficiency, … (Desoete, Roeyers and De Clercq, 2004). By giving an overview of the leading definitions and terminology for mathematical disabilities, the authors of chapter 2 want to contribute to a

better adjustment of criteria used in future research. In this chapter, the authors also want to give an overview of different typologies. The assessment of mathematical disabilities is also discussed. Most practitioners make a diagnosis based on observational measures and criterion-based tests. Those tests evaluate whether or not the age-appropriate goals for mathematical education are reached. However, a good assessment of a mathematical disability has to provide children, school, parents and practitioners with a solid base for remediation. The authors present the TEDI-MATH (Grégoire, Noël and Van Nieuwenhoven, 2003), a diagnostic battery that was recently developed. In contrast to the criterion-based tests, this test results in a profile of the strengths and weaknesses of the child, providing practitioners with a more solid base for remediation.

Chapter 3 extensively reviews the research on mathematical disabilities in children with Velo-Cardio-Facial Syndrome. This genetic condition is known to be the most frequent microdeletion syndrome with an incidence of 1/4000 live births. It will be shown that children with VCFS experience difficulties in mathematics. The research in VCFS on the cognitive correlates associated with MD, such as working memory, will be described as well as the brain imaging studies that point to specific deficits in math related brain areas in these children.

However, the reported studies on MD in VCFS still have some methodological shortcomings, such as the selection of appropriate control groups and the lack of taking into account environmental variables, like instructional environment or socio-economic factors. Additionally, some critical remarks on math assessment in these studies can be formulated. These comments may provide some guidelines for future research on MD in genetic syndromes in general and MD in VCFS in particular.

In chapter 4, the general health of adults and juveniles with a visual-perceptual subtype of dyslexia known as Irlen Syndrome (IS) was assessed by a self-administered questionnaire, and the responses were investigated in relation to changes in urinary and plasma biochemistry. The prevalence and severity of a number of the symptoms assessed by self-report for a one-week period showed significant differences when compared to their control peers. Increases in symptoms for the IS subjects indicated possible problems with the dysregulation of the immune system, photophobia, neurocognition, mood and with muscle cramps and twitches. The significant increases in these problems suggested that in IS, reading difficulties were accompanied by reductions in the general “well-being” of the individual. The reported severity of both the IS and the general health symptoms were associated with alterations in the levels of specific plasma lipids and urinary metabolites for the IS cohort. The results suggested that in IS the general health of the individual may be poorer and that these changes, along with the symptoms that define the syndrome, may be associated with anomalous biochemistry. Examination of these associations provides further insight to understanding the aetiology of this learning disability.

Chapter 5 details the skills and deficits of a group of 40 brain tumour survivors. Areas of functioning assessed included reading, IQ, memory, attention and learning. Information on school attendance, peer relationships and mother and teacher perceptions of behavioural, social, physical and educational needs is also presented. The findings point to specific cognitive issues for brain tumour survivors, including compromised verbal skills, IQ, memory and literacy. Information processing skills including attention/concentration, learning and speed of processing are also affected. Results also highlight a shortfall between deficits and remediation. The high prevalence of behavioural, social and emotional problems is also

discussed. Compromised learning ability means that survivors will require special help to acquire new skills and information. Recommendations for such help, including the use of visual aids to support learning and more time to complete tasks both in class and in tests are made.

The review presented in chapter 6 focuses on antidepressant and antipsychotic drug therapy, with some further brief comments about other psychotropic drugs that are used in the management of behavioural problems of patients with learning disabilities and epilepsy. The effect of antiepileptic drugs on behaviour is also discussed in the light of a rational psychopharmacotherapy of patients with epilepsy and learning disabilities.

Chapter 7 discusses reading disorder (RD) and attention-deficit/hyperactivity disorder (ADHD), which are two of the most common neuropsychological problems of childhood. Recent studies indicate that many children have both RD and ADHD and it has been proposed that both conditions can be causally related. The objective of this study was the event-related brain potentials (ERP) recording of ADHD and RD children (8-12 years old) during continuous performance task (CPT), in order to distinguish whether children with ADHD only and RD only demonstrate common or specific deficits in attention and/or inhibition processes measured both behaviorally and electrophysiologically. CPT included five conditions: Go, No Go, Warning, False Go and Frequent stimuli. Behavioral data showed that there were no between-groups differences in hits nor omission or commission errors, but in reaction times to hits control subjects showed significantly shorter times than the other two groups. The electrophysiological results showed that P300 amplitude was larger for Go than for No Go condition in Control and RD groups, but not in the ADHD group. For No Go condition, control group showed higher P300 amplitudes as compared to RD and ADHD. However, the electrophysiological responses of these later groups were different, since ADHD showed larger amplitudes than RD to No Go and False Go stimuli, while RD displayed greater P300 amplitudes as compared to ADHD in Go and Warning stimuli. It is concluded that ADHD children present deficiencies in both the allocation of attentional resources and in the inhibitory processes, while in RD children the main problem is the scarce amount of attentional resources devoted to information processing.

Between 5 and 15% of elementary-aged children in the United States experience difficulties in reading, mathematics, and writing that cannot be explained by sensory deficits, low intelligence, or economic hardship. Moreover, these deficits are closely linked with long-term school failure. The implementation of instructional feedback interventions has been demonstrated to be effective in addressing the range of problems contributing to children's reading, mathematics, and writing difficulties. In chapter 8, the authors describe how instructional feedback can be used to improve children's academic skill development and achievement. They begin by reviewing the current educational progress of students enrolled in public schools. Next is discussed the importance of implementing empirically-supported practices to improve children's academic skills. The theoretical framework associated with instructional feedback is also reviewed, and a rationale for the use of this method with children at-risk for or diagnosed with learning disabilities is provided. Subsequently, a number of different types of instructional feedback interventions that have been developed for children diagnosed with learning disabilities or learning problems is reviewed and evaluated. Finally, the authors examine recent empirical applications that have attempted to isolate the informational component of instructional feedback with heterogeneous groupings of children.

Chapter 9 presents a study aimed to find electrophysiological differences in semantic and syntactic processes between normal readers and PR during reading tasks, through the study of two language event-related potentials (ERP): N400 a component related to semantic processing and P600 related to syntactic processing. This study provides neurobiological basis of the semantic and syntactic deficits that PR show during reading. Poor Readers (PR) constitute the greater population of reading-disabled children in our country. According to Rayner and Pollatsek (1989), PR have milder reading difficulties than dyslexics, a normal IQ and their scores in standardized reading test are between one and two standard deviations below normal readers. Although scarcely studied, it is known that semantic and syntactic abilities are affected besides their deficiencies in phonological and working memory processes in both PR and dyslexics, though not merely a consequence of them.

The purpose of the study presented in chapter 10 was to examine prospectively usefulness of Early Childhood Inventory-4 (ECI-4) in identifying Attention Deficit Hyperactivity Disorder (ADHD) in a sample of children under 6 years of age who were evaluated in school settings and compare results with those of Conners Rating Scales-Revised (CRS-R) 6 months later. The sample consisted of 34 healthy children (20 boys, 14 girls) prospectively followed-up. Frequency of children fulfill ADHD criteria in ECI-4 parent scale was 17%, and in teacher scale was 32%. Frequency of children fulfill ADHD criteria in parent CRS-R was 20%, and for teacher questionnaire was 23%. Correlations were significant among teacher ECI-4 and both teacher and parent CRS-R scales. Sensitivity and specificity of teacher and parent ECI-4 scales were not good. In summary these facts support partially the use of ECI-4 screening of ADHD in Spanish–speaking preschool children.

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Chapter 1

CORTICAL ASYMMETRY AND LEARNING EFFICIENCY: A DIRECTION FOR THE REHABILITATION PROCESS

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ABSTRACT

In numerous reviews that have appeared in the literature of learning disabilities over the past 100 years, Hynd & Willis (1988) concluded that by 1905 the number of observations that had emerged from the evolving literature was such that a number of tentative conclusions could be offered. Overall, the literature by 1905 supported the following: (1) reading disability (congenital word blindness) could manifest in children with normal ability, (2) males seemed to be more often affected than females, (3) children presented with varied symptoms, but all suffered a core deficit in reading acquisition, (4) normal or even extended classroom instruction did not significantly improve reading ability, (5) some reading problems seemed to be transmitted genetically, and (6) the core symptoms seemed similar to those seen in adults with left temporo-parietal lesions.

INTRODUCTION

While no one would contest the idea that learning disabilities may differentially manifest in many areas of learning, including arithmetic, writing spelling, and so on, there is little doubt that it is with reading disabilities, or dyslexia, where most researchers have concentrated their efforts. For this reason and because so many researchers from

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Neuropsychology, neurology, and neurolinguistics have focused their efforts on reading disabilities, we will examine this literature in an attempt to draw some meaning from the volumes of research that have investigated brain-behavior relationships in this most common of learning disabilities. In fact, an understanding of this literature and the theoretical ideas concerning the meaning of lateralized function and potentially associated deviations in brain morphology may well assist future scholars in their investigation of the neurobiological basis of other forms of learning disabilities.

As the early case studies suggested, learning disabilities have always been thought to have a neurological origin and present definitions of learning disability reflect this perspective (Wyngaarden, 1987). However, the literature supporting this perspective has generated a great deal of controversy. As Golden (1982) and Taylor and Fletcher (1983) have pointed out, much if not most of the literature through the early part of the 1980s was correlational in nature. For example, some research indicates that reading-disabled children have an increased incidence of electrophysiological abnormalities (Duffy *et al.*, 1980) and perhaps differentially so in subtypes of reading disabilities (e.g., Fried *et al.*, 1981). Soft signs are also more frequently found in reading-disabled children (Peters *et al.*, 1975) and few would argue that reading disabled children have a higher incidence of left- or mixed handedness (Bryden & Steenhuis, 1991). Further, reading-disabled children are often inferred to have weak or incomplete laterality, as evidenced on perceptual measures such as dichotic listening (Obrzut, 1991). In fact, volumes summarizing the research in this area have been written (Bakker & van der Vlugt, 1989; Gaddes, 1985; Kershner & Chyczij, 1992; Obrzut & Hynd, 1991), but we are stiff to a significant degree left with inferential or correlative evidence supporting the presumption of a neurological etiology for learning disabilities. Typical of such inferential evidence were studies that found that children with learning disabilities performed more poorly than normal children on any given task (cognitive or perceptual) but did better than children with documented brain damage (e.g., Reitan & Boll, 1973). Needless to say, the inference was often made that the learning-disabled children suffered "minimal brain dysfunction" because their level of performance was somewhere between normality and known brain damage. This was clearly an inference and while not without merit theoretically, it did not directly correlate a known neurological deviation of any kind (e.g., developmental, traumatic) with observed behavioral or cognitive deficits, as we might find in learning-disabled children.

This absence of confirming evidence is certainly not due to a shortage of theories or research, however. Historically relevant is the theory of Orton (1928) who proposed that as children become more linguistically competent, the left cerebral hemisphere becomes progressively more dominant for speech and language. He believed that motor dominance and its evolution in the developing child reflected this process of progressive lateralization. Consequently, according to Orton, children who had mixed cerebral dominance, as might be reflected in poor language skills, reading words or letters backward and inconsistent handedness, were most likely delayed in cerebral lateralization and therefore neither cerebral hemisphere, particularly the left, was dominant for linguistic processes. While decades of research documented that learning-disabled children were indeed deficient in language processes, especially phonological coding, the model of progressive lateralization has not been supported by the research (Benton, 1975; Kinsboume & Hiscock, 1981; Satz 1991).

Most of the development and normal function of the cerebrum is dependent on subcortical structures especially the *cerebellum*and *basal ganglia*. A failure to develop and or

a dysfunction in these areas can affect both the nonspecific arousal system as well as specific transfer of information in the brain. Dysfunction in these areas will usually result in specific motor and sensory symptoms that are commonly seen in children with cognitive or behavioral disorders. These brain regions are often seen to be underactive or atrophied as well in these children. These cortical loci have been shown to be connected with the *prefrontal cortex*, which have also often been noted to be underactive or atrophied in children with the neurobehavioral developmental disorders. The underactivity and or atrophy is usually either restricted to the right or left side of the sub-cortex and cortex (Melillo & Leisman, 2004).

An imbalance of activity or arousal of one side of the cortex or the other can result in a functional disconnection syndrome similar to what is seen in split-brain patients, this could be an underlying source of many if not all of the symptoms that we see with children with behavioral and cognitive disorders. For example, post-mortem examinations have indicated structural differences between the brains of good and impaired readers. High concentrations of micro-dysgenesis are noted in the left temporoparietal regions of dyslexic brains. The concentration is most evidenced in the *planum temporale* region (Galaburda *et al.,* 1985; Kaufman & Galaburda, 1989; Duane 1989). These micro-dysgeneses seriously impair the normal pattern of architecture of dyslexics and remove the asymmetry normally observed between the enlarged language areas of the left temporoparietal region and the smaller homologous areas of the right hemisphere (Galaburda *et al.,* 1985; Leisman & Ashkenazi, 1980). The capacity for language is generally correlated with a significant development in the magnitude of the left temporoparietal region and an attrition of neurons in the right hemisphere. These neuronal casualties may produce the observed asymmetry between corresponding areas in the left and right hemispheres (Geschwind & Levitsky, 1968; Leisman & Ashkenazi, 1980). The relative symmetry in the dyslexics' brains might reflect their impaired linguistic development.

In one study, (Leisman, 2002; Leisman, and Melillo, 2004)) left parieto-occipital EEG leads recorded a frequency spectrum in dyslexics that was consistently different from the spectrum obtained from normals. It is suggested that these effects represent significant differences in the functional organization of these areas. EEG coherence values indicate that normals have significantly greater sharing between hemispheres at symmetrical locations. Dyslexics demonstrate significantly greater sharing within hemisphere than do normals as evidenced in Table 1. The data supports the notion that developmental dyslexia is a functional hemispheric disconnection syndrome. Other conditions in the spectrum of disorders that we are discussing yield similar results.

This spectrum of childhood disorders that we are discussing generally relates to an increase or decrease in activation of the brain and the balance of activation between brain regions. These conditions result from two primary system effects: 1) primary arousal deficit or imbalance, and 2) a specific activation deficit, imbalance, or asynchrony. The brain is driven by sensory input. We know that the brain receives more simultaneous sensory input than it can possibly consciously process (Heilman, 1995; Leisman, 1976; Broadbent, 1958; 1965) In general the more stimulation a brain cells receive the better their function allowing it to process more information faster, for longer periods of time (Venables, 1989; Pascual & Figueroa, 1996; Szeligo & Leblond, 1977; van Praag *et al.,* 2000). Therefore all sensory input is important although not all of it can be consciously processed and perceived. In fact, without subconscious baseline stimulation higher conscious processing of sensory stimuli would be difficult if not impossible.

Table I. Average frequency (in Hz), power (in dB), left-right asymmetry of power (in dB) between hemispheres and within hemisphere coherence values at P_3-O_1/P_4-O_2 locations for dyslexics and normals

	Dyslexic					Normal				
S	Freq (Hz)	Power (dB)	L-R (dB)	Bilat. Coher.	W/in Coher.	Freq. (Hz)	Power (dB)	L-R (dB)	Bilat. Coher.	W/in Coher.
1	09.2	12	-03	--	1.1	09.2	28	--	--	0.8
2	10.4	21	-04	--	1.8	10.8	24	--	2.4	--
3	11.7	22	10	--	2.4	12.7	18	--	1.9	--
4	09.8	18	04	--	1.6	10.9	20	-4	1.3	--
5	10.8	17	03	--	1.4	08.6	16	--	1.9	--
6	10.6	24	-01	--	0.8	08.9	08	--	1.8	--
7	10.6	28	-05	--	1.5	11.2	11	--	2.4	--
8	11.2	12	-07	--	2.1	11.7	13	-2	1.5	1.8
9	12.0	19	-04	--	1.9	10.0	12	--	1.3	--
10	09.8	14	--	0.7	0.6	10.7	15	-1	1.3	0.9
11	10.8	25	-02	--	1.0	10.6	11	--	1.2	1.4
12	11.7	22	--	1.0	--	12.0	09	--	0.8	1.1
13	08.7	13	-01	--	0.9	11.7	07	--	1.0	--
14	09.0	27	08	--	2.1	08.9	11	--	1.9	--
15	10.7	13	-04	--	2.4	09.5	10	--	1.7	0.6
16	10.3	08	-06	--	1.8	08.8	11	-2	2.1	--
17	09.5	22	-07	--	2.0	08.6	14	--	1.4	--
18	12.2	20	-07	--	1.9	09.3	09	--	1.8	--
19	11.9	09	-01	--	0.9	12.4	12	--	1.9	--
20	08.4	15	-04	--	1.6	11.6	10	--	0.9	--

Before higher brain centers can develop, the lesser supportive brain structures must develop. In the cortex, Luria (1973) thought that lateralized cortical functions progress from primary cortical areas to secondary and tertiary areas as the child matures (Luria, 1973). Going back even further we see that development of cortical areas and the cortex itself are dependent on the anatomic and functional development of subcortical areas especially the *cerebellum* and the *thalamus*. Studies suggest that intact *cerebellar* functioning is required for normal cerebral functional and anatomical development (Rae *et al.*, 1998; Llinas, 1995). The same has been seen for the *thalamus* - that intact *thalamic* function is necessary to cortical development and function (Castro-Alamancos, 2002; Scannell *et al.*, 1999; 2000; Gil *et al.*, 1999; Albe-Fessard *et al.*, 1983; Kalivas *et al.*, 1999). Developmental dysfunction of the same brain areas as seen in acquired disorders such as post-traumatic aphasia may be the basis of developmental learning disabilities and neurobehavioral disorders (Dawson, 1996; 1988; Obrzut, 1991).

As Orton (1928) had indicated, it is generally assumed that persons with learning disabilities have abnormal cerebral organization including atypical or weak patterns of hemisphere specialization (Bryden, 1988; Corballis, 1983; Obrzut, 1991). The developmental lag hypothesis proposed by Lenneberg (1967) suggested that learning-disabled persons are slower to develop basic language skills and demonstrate weak hemispheric specialization for language tasks. In a reformulation of the progressive lateralization hypothesis (Satz, 1991), it may be that subcortical and antero-posterior progressions have a differential developmental

course with learning disabled children and adults compared to control subjects or those with acquired syndromes.

Since learning disabled children exhibit deficient performance on a variety of tests thought to be a measure of perceptual laterality, evidence of weak laterality or failure to develop laterality has been found across various modalities (audio, visual, tactile) (Boliek & Obrzut, 1995). It is thought these children have abnormal cerebral organization as suggested by Corballis (1983) and Obrzut (1991). The basic assumption is that dysfunction in the the central nervous system either prenatally or during early postnatal development, results in abnormal cerebral organization and associated dysfunctional specialization needed for lateralized processing of language function and non-language skills. It is thought that cortical and subcortical dysfunction which results from aberrant patterns of activation or arousal (Obrzut, 1991), inter- and intrahemispheric transmission deficits, inadequate resource allocation (Keshner & Peterson, 1988), or any combination of these may compromise hemispheric specialization in those with cognitive and behavioral deficits (Bolick & Obrzut, 1995).

Development of higher processing areas in the *cerebellar* cortex would develop after other more primary areas. For example, the lateral *cerebellum* would be dependent on proper development of the more midline areas in the inter-medial and medial zones first. Similarly, any region to which lateral *cerebellum* projected would be dependent on the effective development of the lateral *cerebellum* and it in turn would be dependent on the more medial *cerebellar* development. Therefore, if the medial aspects of the *cerebellum* do not develop adequately, then the lateral areas would still grow however, they may be smaller or atrophic, and dysfunction would be expected.

The *cerebellum*is thought to be part of a neuronal system that includes the *thalamus basal ganglia*and *prefrontal cortex* (Thatch, 1980). Anatomic and functional development of the nervous system is dependent on sensory input, which is associated with growth of a given brain area and its associated connectivities with other brain regions. Brain area growth and the capacity to make functional connectivities is highly dependent on: continued regional stimulation and by global stimulation through connected and coordinated function. If specific regions are inadequately stimulated, then we may see failure of anatomic or functional development in that region with a preservation of basic lower level functionality. Higher functions that depend on greater areas of integrated stimulation may be lost or dysfunctional. If the sensory loss develops after a *critical period,* these areas may still be smaller due to atrophy or reverse plasticity, with either global or specific effects depending on the modality of dysfunction. In children with learning disabilities or affective disorders, there are specific areas of the nervous system that have been noted in imaging studies to be smaller than normal (von Plessen *et al.,* 2002; Frank & Pavlakis, 2001; Larsen *et al.,* 1990). Most often, these areas involve the *prefrontal cortex*, *basal ganglia*, *thalamus,* and *cerebellum.*

Some neurophysiologists regard the central nervous system as partly a *closed* and part *open* system (Llinas, 1995). An open system is one that accepts input from the environment, processes it, and returns it to the external environment. A closed system suggests that the basic organization of the central nervous system is geared toward the generation of intrinsic images and is primarily self-activating and capable of generating a cognitive representation of the outside environment even without incoming sensory stimuli. Although it is possible that a certain level of activation or stimulation will be intrinsic to single neuronal cells and the nervous system as a whole, this stimulation does not seem adequate to sustain a conscious,

awake, individual. Behaviorally, arousal is a term used to describe an organism that is prepared to process incoming stimuli. From a physiologic standpoint, arousal also refers to the excitatory state or the propensity of neurons to discharge when appropriately activated (neuronal preparation). A non-aroused organism is comatose (Heilman, 1995). Therefore, an aroused alert individual that is prepared to process information is in a state dependent on sensory input with an attendant intrinsic excitability. Remove stimulation and the individual will eventually lose conscious awareness and become comatose or at least inattentive. The majority of brain activity associated with arousal comes from the ascending *reticular activating system*. The majority of this activity is relayed by the non-specific *thalamic nuclei* or *intralaminar nuclei*.

All sensory perception is based on the effectiveness of the arousal level of nonspecific, mostly subconscious, activity of the brain. There can be no specific sensory modality perception like vision or hearing without a baseline arousal level. The more stimulation or greater frequency of stimulation the more aroused an individual will be. Low frequency stimulation of midline *thalamic non-specific nuclei* produces inattention, drowsiness, and sleep accompanied by slow wave synchronous activity and so called spindle bursts. High frequency stimulation on the other hand has been shown to arouse a sleeping subject or alert a waking organism (Tanaka *et al.*, 1975; Arnulf *et al.*, 2000; Halboni, 2000). Specific sensory perception and processing is dependent on specific *thalamic* relays, if one of the specific *thalamic* nuclei are damaged such as the *lateral geniculate body*, that specific sensory modality is lost (e.g. blindness) but it does not result in loss of other specific nuclei input like hearing. However, if lesions of the non-specific intralaminar nuclei exist, patients cannot perceive or respond to any input by the specific intact nuclei even though those pathways are intact. In essence, the person does not exist from a cognitive standpoint (Llinas, 1995).

Luria postulated that the brain was divided into three functional units: 1) the arousal unit, 2) the sensory receptive and integrative unit, and 3) the planning and organizational unit. He subdivided the last two into three hierarchic zones. The primary zone is responsible for sorting and recording incoming sensory information. The secondary zone organizes and codes information from the primary zone. The tertiary zone is where data are merged from multiple sources of input and collated as the basis for organizing complex behavioral responses (Luria, 1973). Luria's dynamic progression of lateralized function is similar to Hughlings Jackson's Cartesian coordinates with respect to progressive function from *brainstem* to cortical regions (Kinsbourne & Hiscock, 1983).

Satz (1991) suggested that developmental invariance describes the lateral (x-axis) dimension of asymmetry, whereas current formulation of equipotentiality and the *progressive lateralization hypothesis* better describes vertical (subcortical-cortical) and horizontal (antero-posterior) progression during infancy and early childhood. Interestingly it has been noted that most research designed to address laterality issues in developmental disabilities (i.e. learning disabilities) has not dealt systematically with subcortical-cortical development or antero-posterior progression, all based on the concept of arousal unit.

The arousal unit is really the *non-specific thalamic nuclei*. We know that arousal is dependent on external and internal environmental sensory input. The largest proportion of subconscious sensory input passes between the *thalamus*, *cerebellum*, and *dorsal column* from slowly adapting receptors found in muscles with a preponderance of slow-twitch fibers - or slowly adapting muscle spindle receptors. The highest percentage of these is found in anti-gravity postural muscles especially muscles of the spine and neck (Guyton, 1986). The

receptors, which provide the major source of input to the brain, only receive sensory information. These receptors only work when muscles are stretched or contracted with gravity being the most frequent and constant sensory stimulus.

In summary, brain development and the adequacy of it continued functioning is dependent on sensory input. Specific sensory perceptual processes like vision and hearing are dependent on non-specific sensory input. This, in turn, creates a baseline arousal and synchronization of brain activity (consciousness). This is a form of constant arousal and is dependent on a constant flow of sensory input from receptors that are found in muscles of the spine and neck. These receptors receive the majority of their stimulation from gravity, creating a feedback loop that forms the basis of most if not all of brain function. Sensory input drives the brain, and motor activity drives the sensory system. Without sensory input the brain cannot perceive or process input. Without motor activity provided by constant action of postural muscles a large proportion of sensory stimuli are lost to further processing. This loop is the *somatosensory system*.

Higher processing is also dependent on the baseline sensory functions. For example, it has been shown that when performing a complex task, it is likely that transfer of motor commands to produce a final output is preceded to some degree, by transfer of information between association areas, which in turn may precede transfer between sensory regions (Banich, 1995).

Actually, there is a growing body of evidence that indicates that very young children, including infants, are lateralized for language processing (Molfese & Molfese, 1986). Thus, none would refute the notion that in the majority of cases language is lateralized to the left cerebral hemisphere. However, while language abilities clearly develop over the course of human ontogeny, language remains lateralized, as it was early in infant development. What may devolve is the capacity for plasticity of function; i.e., the capacity for the other cerebral hemisphere to assume language functions when the dominant hemisphere is severely damaged may decrease significantly with the course of development (Piacentini & Hynd, 1988). What neurological structures or deficient neuropsychological systems underlie the behavioral and cognitive symptoms we associate with learning disabilities, particularly reading disabilities? While there are likely many different ways in which one could begin to address this question, we will approach this question from a neurolinguistic-neuroanatomic perspective. We first present a discussion of the lateralized system of language and associated reading processes and then examine its impact and relation to research that employs brain-imaging procedures to investigate morphologic differences in the brains of reading-disabled children and adolescents. In this fashion we hope to directly tie deviations in lateralized brain processes (e.g., language, reading) to potentially associated deviations in brain structure.

NEUROLINGULSTIC-NEUROANATOMIC MODEL

For over a century, those concerned with reading and language disorders have attempted to correlate observed functional deficits with the location of known brain lesions (Bastian, 1898; Dejerine, 1892; Dejerine & Vialet, 1893; Dejerme & Dejerine-Klumpke, 1901; Geschwind, 1974; Head, 1926; Kussmaul, 1877; Wemicke, 1910). These scholars and others interested in the lateralization and localization of language and reading processes contributed

to a literature that resulted in a neurolinguistic model of language and reading referred to by some as the Wernicke-Geschwind model (Mayeux & Kandel, 1985). While Wernicke and Dejerine deserve the most credit for the development of this model, it is clear that Geschwind (1974) did much to revive interest in the perspective first proposed in part by Bastian (1898), Liepmann (1915), Marie (1906), and others, whose ideas were controversial even when they were first proposed. As Head (1926) suggested over 60 years ago, "localization of speech became a political question; the older conservative school, haunted by the bogey of phrenology, clung to the conception that the 'brain acted as a whole,' whilst the younger liberals and Republicans passionately favored the view that different functions were exercised by the various portions of the cerebral hemispheres" (p. 25).

Even among the "diagram makers" (Head, 1926) controversy existed. For example, Bastian (1898) argued strongly against the popular perspective advocated by Dejerine whose views so influenced Geschwind in his thinking. Bastian proposed that bilateral visual word centers existed in the brain, each of which was involved in visual perception, low-level feature analysis, and cross-modal integration with the central language centers. Dejerine's views prevailed, however, as the accumulation of case studies supported the notion that there was indeed a left-lateralized "word center," most notably, it seemed, in the region of the angular gyrus. Figure 1 graphically contrasts Dejerine and Bastian's views on the posterior cortex involved in reading. Based on the contributions of Broca, Wernicke, and the others noted above, a more complete neurolinguistic model of language and reading evolved. This model presupposes that visual stimuli such as words are registered in the bilateral primary occipital cortex, meaningful low-level perceptual associations occur in the secondary visual cortex, and this input is shared with further input from other sensory modalities in the region of the angular gyms in the left cerebral hemisphere. This sequential neurocognitive process presumably then associates linguistic-semantic comprehension with input from the region of the angular gyms; a process which involves the cortical region of the left posterior superior temporal region, including the region of the *planum temporale*. The process is completed when interhemispheric fibers connect these regions with Broca's area in the left inferior frontal region. Figure 2 presents this model, and the Dejerine's theory of the left lateralized "word center" seen in the posterior aspect of the figure.

It was Geschwind (1974), of course, who revived interest in this neurolinguistic-neuroanatomic model. He contributed significantly, however, by focusing attention on the natural left-sided asymmetry of the region of the *planum temporale*. Reports by early investigators (Flechsig, 1908; von Economo & Horn, 1930) encouraged Geschwind and Levitsky (1968) to investigate asymmetries associated with the region of the *planum temporale*. They examined 100 normal adult brains and found that the region of the *planum temporale* (the most posterior aspect of the superior temporal lobe) is larger on the left in 65% of brains, whereas it is larger on the right in only 11 percent of brains. These findings were taken as evidence of a specialized and asymmetric neuroanatomical region in support of language functions. Studies by other investigators documented the finding of plana asymmetry in both adult and infant brains (Kopp *et al.*, 1977; Rubens, Mahuwald, & Hutton, 1976; Wada, Clarke, and Hamm, 1975; Witelson & Pallie, 1973). Figure 3 shows the left-sided asymmetry typically found in normal brains that is thought to subserve the evolution of higher-order neurolinguistic processes.

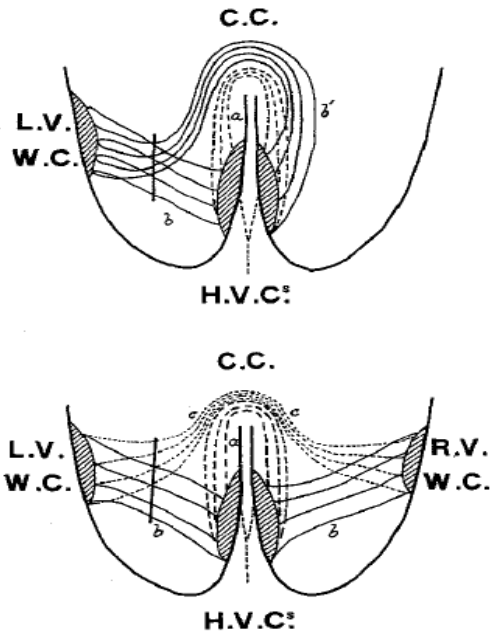

Figure 1. A comparison o Dejerine's and Bastain's views on the neuroanatomical basis of "pure word blindness" as presented by Bastian (1898). (Above) A simplified diagram representing Dejerine's views of the mode of production of pure word blindness. The dark line indicates the site of a lesion that cuts off the left visual word center (L.V.W.C.) from the Half vision center (H.V.C.) of each side. (Below) A diagram representing Bastian's views of the mode of production of pure word blindness. C.C., corpus callosum.

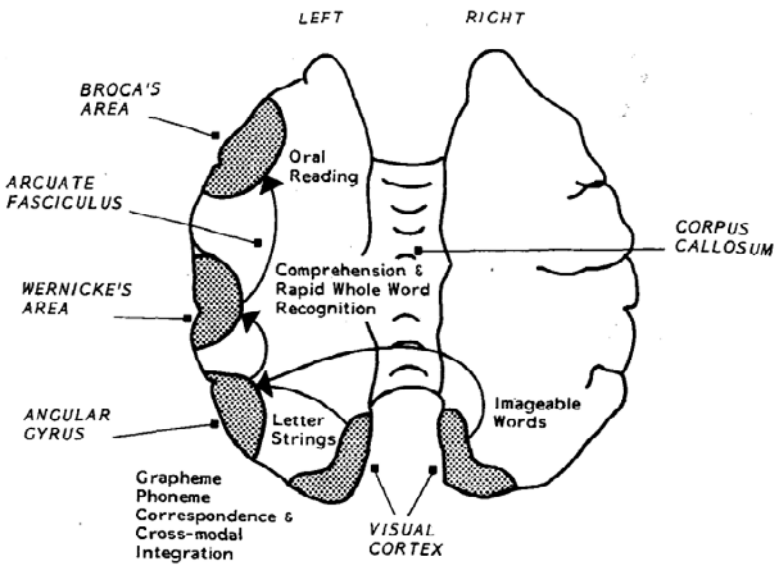

Figure 2. The brain as viewed in horizontal section. The major pathways and cortical regions thought to be involved in reading are depicted. neurolinguistic processes important in reading are also noted.

The research that was encouraged by the findings of Geschwind and Levitsky (1968) was significant in that other morphologic asymmetries in the human brain were soon reported. For example, Weinberger and colleagues (1982) found evidence that in approximately 75% of normal brains the right frontal volume (R) exceeds that of the left frontal cortex (L). Also this pattern of L < R asymmetry seems evident in fetal development as early as 20 weeks. Other documented asymmetries include the left anterior speech region (*pars opercularis* and *pars triangularis* of the third frontal convolution) favoring the left side (Falzi *et al.*, 1982) and cytoamhitectonic asymmetries favoring the left inferior parietal lobe (Eidelberg & Galaburda, 1984), the left auditory cortex (Galaburda & Sanides, 1980), and the posterior thalamus (Pidelberg & Galaburda, 1982).

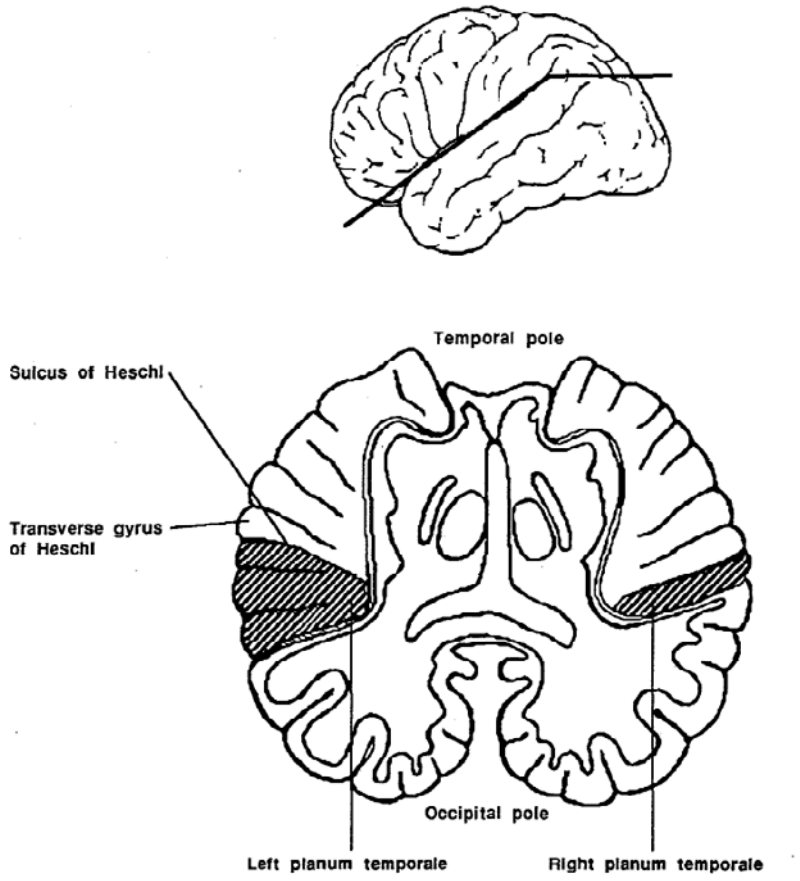

Figure 3. A graphic representation (top) of a slice up the sylvian (lateral) fissure exposing the posterior portion of the superior temporal region. The *planum temporale* is shaded bilaterally (bottom) and it can be seen that it is generally larger on the left.

Based on these as well as other research findings, Geschwind (1974, 1984) and especially Geschwind and Galaburda (1985a-c) argued that these natural asymmetries may be associated in a meaningful manner with language processes and, in cases of reversed asymmetry or symmetry, they ‘may underlie the deficits we observe in severe reading disabilities. While the theory outlined by Geschwind and Galaburda (1985a-c) addresses the possible relations between male gender differentiation, the effects of testosterone on neuronal assemblies, and

correlated asymmetries in brain morphology, immune function, and left-handedness, may indicate that deviations in natural brain asymmetries may be related to the deficient linguistic and reading processes observed in reading disabled children. Thus, in this context, the remainder of this chapter will address the brain-imaging literature and examine the findings in relation to whether or not evidence exists in support of the notion that deviations in natural asymmetries in the language-reading system in the brain are indeed related in some fashion to the cognitive or behavioral deficits observe in these children.

BRAIN IMAGING

Many methodologies have been employed to investigate laterality and asymmetries in human performance. Certainly, visual half-field and dichotic listening experiments have assisted us greatly in better understanding perceptual asymmetries that underlie linguistic and visuospatial perception. Dual-task paradigms have helped develop a better understanding of the lateralization of hemispheric attentional mechanisms and handedness-manual preference inventories have likewise helped in documenting variability in human laterality. All of these methodologies rely on the recording of a behavioral response that in turn leads to a measure of laterality. The documentation of morphologic asymmetries in the human brain that seemed to favor the left hemisphere central language zones encouraged speculation that variability in these patterns of asymmetry might be related to the behavioral deficits we see in such conditions as severe reading disability. Geschwind and his colleagues deserve much of the credit for encouraging this perspective. In this context then, measures of manual preference or perceptual asymmetries might still be of interest but they could not provide a window from which to actually view the brain and its associated morphology.

Computed tomography (CT) and magnetic resonance imaging (MRI) were obviously technologic advances that could help researchers examine directly structure-function relations in living humans. CT, of course, is considered an invasive procedure, as there is some limited exposure to radiation, whereas with MRI scans there are no known risk factors. Until MRl became more readily available, CT was the method employed to examine deviations in normal patters of asymmetry in the brains of reading-disabled children and adults. CT studies typically employed a scan between 0 and 25 degrees above the acanthomedial line to examine for posterior asymmetries. With the increased sophistication of MRI scanning procedures it became possible to obtain thinner slices and extreme lateral sagittal scans were used to examine sulcul topography as well. Most s canning facilities now have the capability to obtain three-dimensional volumetric scan data so that later reconstructions can be made on any plane desired. These technological advances have been accompanied by very significant methodological challenges with regard to head positioning, using a standardized grid system to normalize data acquisition across scans, and other difficulties in defining morphologic boundaries that may have functional significance. Nonetheless, these studies have been revealing and have encouraged increasing interest in using brain-imaging procedures to investigate many issues important to the study of lateralized functioning.

Table II. Brain imaging studies of subjects with developmental dyslexia

Study	Type	No. of subjects	Mean age (yr)	Diagnostic criteria	Conclusions
Hier et al. (1978)	CT	24	25	Less than 5th-grade reading level on Gray Oral Reading Test or > 2-yr delay in reading while in school	Dyslexic subjects with reversed posterior asymmetry had lower verbal IQ 33% had normal L>R posterior asymmetry; 67% had symmetry or reversed (L<R) posterior asymmetry
LeMay (1978)	CT	27 dyslexic subjects[a] 317 controls	NR	NR	33% of dyslexic subjects had normal (L>R) posterior asymmetry compared to 70% of right-handed controls Left-handed controls evidenced more symmetry and reversed (L<R) asymmetry of posterior region
Leisman and Ashkenazi (1980)	CT	8 dyslexic subjects 2 controls	8.2—dyslexic subjects 7.6—normals	NR	100% of dyslexic subjects had symmetry or received asymmetry (L<R) of posterior region
Rosenberger and Hier (1980)	CT	53	6–45 (range)	Two grade levels below actual grade; large verbal-performance IQ discrepancy	42% of dyslexic subjects had reversed asymmetry (L<R) of posterior region Asymmetry index correlated with verbal-performance IQ discrepancy ($r = .38$, $P < .02$)
Haslam et al. (1981)	CT	26 dyslexic subjects 8 controls	11.7—dyslexic subjects 9.8—controls	Reading performance at least 2 yr below expected level based on IQ	46% of dyslexic subjects showed normal (L>R) posterior asymmetry while 87% controls did No relationship between IQ and posterior symmetry or asymmetry
Rumsey et al. (1986)	MRI	10	22.6	Childhood history of reading disability; median Gray Oral Reading Test was 3.7 grade equivalent	90% of dyslexic subjects showed symmetry of posterior regions
Parkins et al. (1987)	CT	44 dyslexic subjects 254 controls	57	Childhood history of reading and spelling disability, psychometrc evidence of dyslexia	Concluded that reversed posterior asymmetries are not characteristic of right-handed dyslexic subjects, but left-handed dyslexic subjects may evidence more symmetry
Larsen et al. (1990)	MRI	19 dyslexic subjects 19 normals	15.1—dyslexic subjects 15.4 – controls	Highly significant difference between normals and dyslexic subjects in word recognition; selected prior to study by schools as dyslexic	Measured the patterns of asymmetry in the region of the planum temporale: 70% of dyslexic subjects evidenced symmetry, while only 30% of nondyslexic subjects did All dyslexic subjects with plana asymmetry demonstrated significant phonological coding deficits
Hynd et al. (1990)[b]	MRI	10 dyslexic subjects 10 ADDH children 10 normals	9.9—dyslexic subjects 10.0—ADDH children 11.8—normals	IQ ⩾85, positive family history, reading achievement ⩾20 standard score points below full-scale IQ on tests of word recognition and passage comprehension	Both dyslexic subjects ADDH children had smaller right frontal widths (more frontal symmetry than normals) 70% of normal and ADDH children demonstrated L>R plana asymmetry, while only 10% of dyslexic subjects did; plana symmetry or reversed asymmetry seems characteristic of dyslexia
Semrud-Clikeman et al. (1991)	MRI	Same as Hynd et al. (1990)	Same as Hynd et al. (1990)	NR	Frontal width symmetry/reversed asymmetry (L⩾R) associated with very significant delay in word attack skills Symmetry/reversed asymmetry of plana associated with poor confrontational naming, rapid naming, and passage comprehension
Leonard et al. (1993)	MRI	9 dyslexic subjects 10 relatives 11 controls	15–65 6–63 14–52	Primarily by clinical report and history	Dyslexic subjects had exaggerated left plana asymmetry for the temporal band and right asymmetry for the parietal bank Higher incidence of cerebral anomalies bilaterally

Modified from Hynd and Semrud-Clikeman (1989)

Key: ADDH, attention-deficit hyperactivity disorder; NR, not reported.

[a] LeMay (1981) used all subjects of Hier et al. (1978) adding three of her own in addition to the controls.

[b] Semrud-Clikeman et al. (1991) employed these subjects to examine the relationship between deviations in patterns of brain morphology and neurolinguistic ability in developmental dyslexics.

As can be seen in Table II, at least eleven studies using either CT or MRI have been conducted to examine whether or not deviations in normal patterns of asymmetry in brain morphology are associated with the manifestation of reading disabilities. The first such study was reported by Hier and colleagues (1978) who employed CT to investigate posterior asymmetries in 24 dyslexic subjects. They found that only 33 percent of the dyslexic group had a wider left posterior region while 67 percent had either symmetry or reversed asymmetry of the posterior region. Since fully 66 percent of the normal population is expected to show the expected L > R asymmetry, this lower incidence among the dyslexic group was taken as support for Geschwind's (1974) idea that patterns of asymmetry were meaningfully associated with linguistic functioning.

In a further study, Rosenberger and Hier (1980) found that a brain asymmetry index correlated with verbal performance intelligence quotient (IQ) discrepancies, whereas lower verbal IQ was correlated with symmetry or reversed asymmetry in the posterior region in the dyslexic subjects. This study actually was the first to examine whether there was any psychometric or behavioral relationship between asymmetry patterns and performance. In this respect this study was unique and an entire decade elapsed before several new studies also examined behavioral relationships to brain morphology data Thus, most of the early literature was characterized by examining the rather straightforward issue as to whether there was any deviation from normal patterns of brain asymmetry in subjects with severe reading disability. In 1981, Haslam and associates found in their sample of dyslexic subjects that 46 percent had L > R asymmetry similar to the normals, but in contrast to Rosenberger and Hier (1980), no relationship was found with regard to verbal ability. As Hynd and Semrud-Clikeman (1989) have pointed out, however, the-criteria employed by Haslam and colleagues for defining language delay were less strict than in the Rosenberger and Hier study. Nonetheless, Haslam's group (1981) did note that fewer dyslexic subjects had the normal L > R posterior asymmetry.

The mid-1980s marked a time of transition in that fewer CT studies were reported with increasingly more studies employing MRI procedures as MRI scanners became more available to the research community. In fact, the last CT study reported was by Parkins *et al.* (1987) who found that there existed some relationship of handedness to deviations from normal patterns of asymmetry by dyslexic subjects. They found in their older adult sample (mean age, 57 years) that symmetry of the posterior region was characteristic only in the left-handed dyslexic subjects. The results of this study are unusual because previously and in the studies to follow, handedness may have differentiated the normal from the severely reading-disabled sample, but no relationship was ever reported with handedness. The mean age of this sample is also unusual as these were reading-disabled adults who may represent an unusual part of the reading disability spectrum in that their reading disability persisted to such a severe degree well into advanced adulthood. Most other studies typically employed subjects in early adolescence through young adulthood.

The first reported MRI study was in 1986 by Rumsey and associates who found in their brief report that 90 percent of the dyslexic subjects showed evidence of posterior asymmetry. In a sense, this study was typical of the rather unsophisticated methodology that characterized the studies at that tie in that determination of asymmetry, symmetry, and reversed asymmetry of the posterior region most often relied on the clinical judgment of a radiologist or other expert in reading scans. Rarely were data presented as to the morphometric measurements that were obtained, if any, and for this reason it was difficult to compare results across

studies. About the only conclusion that could reasonably be advanced was that deviations in normal patterns of posterior asymmetry may be found more frequently in the brains of severe reading disabled persons. Based entirely on the Rosenberger and Hier (1980) study, there was limited but tantalizing evidence that symmetry or reversed asymmetry may somehow be associated with poor verbal-linguistic ability as is often found in dyslexic children.

To this point most studies had focused on posterior asymmetries, but theory had continued to emphasize the region of the *planum temporale* as being vitally important in verbal- their four consecutive autopsy cases and reported that the focal dysplasias clustered preferentially in the left superior posterior temporal region by a ratio of 2:I. Thus, there was good reason to shift the attention of researchers away from simple posterior asymmetries toward linguistic processes, particularly phonological coding. In fact, Galaburda *et al.* (1985) summarized attempts at measuring asymmetry of the region of the *planum temporale*. The focal dysplasias, Galaburda and colleagues reported, certainly could not be visualized on MRI scans, but different method could be employed in attempting to measure either the area or length of this region bilaterally in the brains of persons with dyslexia. Leisman & Ashkenazi (1980) present sample CT and Leisman & Melillo (2004) present sample MRI scans showing the anomalous cortex in the dyslexic subjects exemplifying measurement of asymmetry issues in dyslexia.

Two studies employed different methodologies aimed at investigating asymmetries in the region of the *planum temporale* in dyslexic persons. Using MRI to examine the size and patterns of asymmetry in this region in adolescents with dyslexia, Larsen, and colleagues (1990) found that 70 percent of their dyslexic group had symmetry in the region of the plana in contrast to 30 percent of the normals. In addition to the importance of this finding, Larsen *et al.* also found that when symmetry of the plana was present in dyslexia, the subjects demonstrated phonological deficits. They concluded that some relationship may exist between brain morphology patterns and neurolinguistic process, consistent with Rosenberger and Hier's (1980) conclusions.

That same year, Hynd *et al.* (1990) also reported a study employing MRI in which the relative specificity of patterns of plana morphology were investigated in relation to a population of normal controls and clinic control children. In this case the clinic control group comprised children with attention-deficit hyperactivity disorder (ADHD). For this reason, the study was unique in that of all studies reported previously, none had included a clinic contrast group but rather compared dyslexic subjects only with normal controls. While such an approach has value in determining whether a line of investigation might be productive, the results only suggested differences from normals. There was no way to address the specificity of deviations in brain morphology in relation to the behavioral deficits seen in any one clinical syndrome such as reading. Based on the previous literature, it was hypothesized that if differences existed in the brains of the dyslexic children in the region of the plana, similar differences would not be evident in the brains of the ADHD children who were carefully diagnosed so that this group did not include children with reading or learning disabilities.

Similar to Larsen *et al.* (1990), Hynd *et al.* (1990) found that the dyslexic group was characterized by either symmetry or reversed asymmetry (L < R) of the plana. Underscoring the importance of this region scientifically, they found that in 70% of the normals and ADDH children, L > R plana asymmetry existed. This is what would be expected according to the normative data provided originally by Geschwind and Levitsky (1968). Fully 90% of the dyslexic children demonstrated symmetry or reversed asymmetry of the plana. In a follow-up

study, Semrud-Clikeman and colleagues (1991) reported that symmetry and reversed asymmetry of the *planum temporale* was associated with significant deficits in confrontational naming, rapid naming, and neurolinguistic processes in general.

If one compares the Larsen *et al.* (1990) and Hynd *et al.* (1990) studies, differences seem evident in the way in which the plana were measured. Hynd *et al.* (1990) measured the length of the plana on extreme lateral sagittal MRI scans. Larsen *et al.* (1990), however, took measurements from sequential scans so that a measurement of area could be derived. Both studies found that significant indices of symmetry or reversed asymmetry characterized the brains of dyslexic children even though different methodologies were employed. A point to derive from this discussion is that there are no agreed-upon standardized methodologies, although the method employed by Larsen *et al.* (1990) most likely provides more reliable data. Further, in examining the literature regarding the neuroanatomical morphology of the ilana, one quickly realizes that there may be different sulcul patterns associated with whether or not a parietal bank of the *planum temporale* exists.

In a study reported by Leonard *et al.* (1993), the morphology of the posterior superior temporal region was examined bilaterally including the relative contribution of the temporal and parietal banks to an asymmetry index. The results of this study are particularly revealing in several ways. First, it turns out that nearly all dyslexic subjects and normals demonstrated a natural leftward asymmetry in the temporal bank and a rightward asymmetry in the parietal bank. When they examined intrahemispheric asymmetry, some dyslexic subjects had an anomalous intrahemispheric asymmetry between the temporal and planar banks in the right hemisphere because of an increased proportion of the plana being in the parietal bank What this suggests is that consideration must be given to measuring both the temporal and parietal banks of the *planum temporale* and the relative contribution of both banks bilaterally in deriving asymmetry indexes. To quickly illustrate this issue the reader may wish to refer to Figure 3, which illustrates the typical fashion in which the plana were described in the literature. By looking at the figure at the top where the slice location is noted, one can see at the end of the sylvian fissure where the slice line cuts horizontally that there is a small ascending ramus that is actually part of the planum. By not including this parietal aspect in lateral measures of asymmetry, the Larsen *et al.* (1990) and Hynd *et al.* (1990) studies were incomplete, although at the time they were published they were excellent studies. Finally, the Leonard *et al.* (1993) study documented that the dyslexic persons were more likely to evidence anomalies such as missing or duplicated gyri bilaterally in the region of the posterior end of the lateral fissure. These cerebral anomalies most likely evolve somewhere between the 24 and 30th week of fetal gestation when gyration occurs and represent a neurodevelopmental anomaly possibly related to a genetic etiology.

What does this literature suggest about cerebral morphology and lateralized function in reading-disabled or dyslexic children? First, it suggests that asymmetry may indeed be characteristic of most normal brains. Second, in the region of the *planum temporale* there may be an increased incidence of symmetry or reversed asymmetry if one only measures the temporal bank. If one measures the bilateral temporal and parietal banks in the dyslexic group one may actually end up with these persons having more leftward asymmetry because of intrahemispheric variation in the right hemisphere, at least according to Leonard *et al.* (1993). As the Leonard *et al.* (1993) study clearly indicates, measuring highly variable brain regions in different subject groups is fraught with complications, and decisions that must be made in terms of what to measure can dramatically influence outcomes. Finally, as Rosenberger and

Hier (1980) first suggested, there may indeed be relationships between deviations in brain morphology and neurolinguistic processes. The Larsen *et al.* (1990) and Semrud-Clikeman *et al.* (1991) studies provide further support for this important aspect of the theory advanced by Geschwind (1974,1984).

RECENT ADVANCES AND THE FUTURE AGENDA IN UNDERSTANDING THE RELATION BETWEEN CORITCAL ASYMMETRY AND LEARNING DISABILITY

There should be little doubt that brain-imaging procedures offer much promise in investigating issues related to possible relationships between brain structure morphology and behavioral observations, whether these observations be clinical or experimental. What needs to be kept in mind however is that across all of these studies in which over 200 subjects have been scanned, not one brain of a reading-disabled subject was judged to be abnormal in structure (other than asymmetry patterns). In other words, no evidence of brain damage was found. This should underscore the important findings of Galaburda and colleagues (1985) who find developmental anomalies in the brains of dyslexic persons. The anomalous cortex identified by Leonard *et al.* (1993) provides further data implicating neurodevelopmental processes as underlying the behavioral symptoms exhibited in dyslexia. It appears that reasonable evidence exists implicating unusual developmental processes sometime during the fifth to seventh month of fetal gestation in dyslexia. Clearly, the exact cause of these neurodevelopmental anomalies is one of the most important unanswered questions.

In autopsy research, Galaburda and his colleagues have been the main contributors to this area of investigation (Galaburda, 1988, 1989, 1993, 1994, 1997; Galaburda & Livingstone, 1993; Galaburda, Menard, & Rosen, 1994). These researchers have found areas of symmetry and asymmetry in normal brains that differ in individuals with reading disabilities. The autopsied brains of individuals with dyslexia show alterations in the pattern of cerebral asymmetry of the language area with size differences, and minor developmental malformations, which affect the cerebral cortex.

The work of Galaburda and colleagues has shown that about two-thirds of normal control brains show an asymmetry; the planum temporale of the left hemisphere is larger that that of the right hemisphere. Between 20% and 25% of normal control brains show no asymmetry, with the remaining having asymmetry in favor of the right side (Best & Demb, 1999). This asymmetry is thought to be established by 31 weeks of gestation (Chi, Dooling, & Gilles, as cited in Best & Demb, 1999), and Witelson and Pallie (1973) have shown hemispheric asymmetry of the planum temporale to be present in fetal brains.

In contrast, the brains of reliably diagnosed cases of developmental dyslexia have shown the absence of ordinary asymmetry; symmetry is the rule in the planum temporale of brains of dyslexic subjects studied at autopsy, and increased symmetry is also found in imaging studies (Best & Demb, 1999; Galaburda, 1993). These findings are relevant since individuals with dyslexia have language-processing difficulties, and reading is a language-related task. Therefore, anatomical differences in one of the language centers of the brain are consistent with the functional deficits of dyslexia.

Because abnormal auditory processing has been demonstrated in individuals with dyslexia, accompanying anatomical abnormalities in the auditory system have also been the focus of autopsy studies, specifically in the medial geniculate nuclei (MGN), which are part of the metathalamus and lie underneath the pulvinar. From the MGN, fibers of the acoustic radiation pass to the auditory areas in the temporal lobes. Normal controls showed no asymmetry of this area, but the brains of individuals with dyslexia showed that the left side MGN neurons were significantly smaller than those on the right side. Also, there were more small neurons and fewer large neurons in the left MGN in individuals with dyslexia versus controls (Galaburda & Livingstone, 1993; Galaburda et al., 1994). These findings are of particular relevance in view of the left hemisphere-based phonological defect in individuals with dyslexia (Tallal, Miller, & Fitch, 1993).

Neuroanantomical abnormalities in the magnocellular visual pathway have been reported (Galaburda & Livingstone, 1993), and these have been postulated to underlie functioning of the transient visual system in individuals with reading disabilities (Iovino, Fletcher, Breitmeyer, & Foorman, 1998). Jenner, Rosen, and Galaburda (1999) concluded that there is a neuronal size difference in the primary visual cortex in dyslexic brains, which is another anomalous expression of cerebral asymmetry (similar to that of the planum temporale) which, in their view, represents abnormal circuits involved in reading.

According to Galaburda, symmetry may represent the absence of necessary developmental "pruning" of neural networks, which is required for specific functions such as language. In other words, the pruning, which takes place in normal controls, does not take place in individuals with dyslexia (Galaburda, 1989, 1994, 1997), thereby resulting in atypical brain structures, which are associated with language-related functions.

MRI (magnetic resonance imaging) studies have substantiated the findings of autopsy studies; namely, individuals with dyslexia do not have the asymmetry or the same patterns of asymmetry of brain structures that is evident in individuals without dyslexia. A number of investigators have demonstrated a high incidence of symmetry in the temporal lobe in individuals with dyslexia. (Best & Demb, 1999; Hugdahl et al., 1998; Kushch et al., 1993; Leonard et al., 1993; Logan, 1996; Rumsey et al., 1996;). Duara et al. (1991) and Larsen, Høien, Lundberg, and Ødegaard (1990) showed a reversal of the normal leftward asymmetry in the region of the brain involving the angular gyrus in the parietal lobe. Dalby, Elbro, and Stodkilde-Jorgensen (1998) demonstrated symmetry or rightward asymmetry in the temporal lobes (lateral to insula) of the dyslexics in their study. Further, the absence of normal left asymmetry was found to correlate with degraded reading skills and phonemic analysis skills.

Logan (1996) reported that individuals with dyslexia had significantly shorter insula regions bilaterally than controls. Hynd et al. (1995) identified asymmetries in the genu of the corpus callosum of individuals with dyslexia and positively correlated both the genu and splenium with reading performance. This supports the hypothesis that, for some individuals with dyslexia, difficulty in reading may be associated with deficient interhemispheric transfer (Leisman & Melillo, 2004). Hynd and his colleagues (Hynd, Marshall, & Semrud-Clikeman, 1991) also reported shorter insula length bilaterally and asymmetrical frontal regions in individuals with dyslexia. The latter was related to poorer passage comprehension. Best and Demb (1999) examined the relationship between a deficit in the magnocellular visual pathway and planum temporale symmetry. They concluded that these two neurological markers for dyslexia were independent.

There has been substantial replication of findings, particularly with respect to the planum temporale. On the other hand, there have been conflicting reports regarding other areas, especially the corpus callosum (Hynd et al., 1995 versus Larsen, Höien, & Ødegaard, 1992). Methodological and sampling differences, such as slice thickness, orientation and position, and partial volume effects may account for this variability. In a review of the literature on the planum temporale, Shapleske et al. (1999) summarized the methodological concerns in operationalizing consistent criteria for anatomical boundaries when measuring the planum temporale and the need to use standardized measures of assessment and operationalized diagnostic criteria. They concluded that dyslexics may show reduced asymmetry of the planum temporale, but studies have been confounded by comorbidity. Njiokiktjien, de Sonneville, and Vaal (1994) concluded that, despite a multitude of developmental factors influencing the final size, total corpus callosal size is implicated in reading disabilities. In a study by Robichon and Habib (1998), in which more rigid methods were applied, MRI and neuropsychological findings of dyslexic adults were correlated and compared with normal controls. Different morphometric characteristics were positively correlated with the degree of impairment of phonological abilities. The corpus callosum of the dyslexic group was more circular in shape and thicker, and the midsaggital surface was larger, particularly in the isthmus.

Neuroanatomical investigations have substantiated what had been surmised from the early traditional studies of acquired brain lesions and associated changes in functions and have brought forward new evidence to support the neurobiological basis of learning disabilities. Advances in neuroimaging have permitted brain dissection "in vivo," a transparent window of brain functions, concurrent with neurological and neuropsychological evaluations. This methodology has supported previous findings and hypotheses while providing new evidence of brain structure/function relationships. Although the neuroanatomical correlates of dyslexia do not answer the question about whether dyslexia is a condition at one extreme in the normal distribution of reading skill (Dalby et al., 1998), the neuroanatomical and neuroimaging studies have provided evidence linking learning disabilities to neurobiological etiology. In a PET scan study, Horwitz, Rumsey, and Donohue (1998) demonstrated that in normal adult readers there was a correlation of regional cerebral blood flow in the left angular gyrus and flow in the extrastriatal, occipital, and temporal lobe regions during single word reading. In men with dyslexia, the left angular gyrus was functionally disconnected from these areas. Gross-Glenn et al. (1991) found regional metabolic activity measured with PET scan to be similar in individuals with dyslexia and those without dyslexia, reflecting that reading depends on neural activity in a widely distributed set of specific brain regions. There were also some differences concentrated in the occipital and frontal lobe regions. In contrast to controls, individuals with dyslexia showed little asymmetry. These findings correspond well with the reduced structural posterior asymmetry observed in the CT scan and postmortem studies. Prefrontal cortex activity was also symmetrical in individuals with dyslexia versus asymmetrical in normal controls. Higher metabolic activity (local utilization rate for glucose) in the lingual area (inferior occipital regions bilaterally) was reported by Lou (1992) with PET studies, and a SPECT (single photon emission computed tomography) scan showed striatal regions as hypoperfused and, by inference, under-functioning.

Numerous studies have attempted to identify the neurological basis of learning disabilities in terms of left–versus right–hemisphere dysfunction. Adult strokes were found to

affect cognitive abilities such as reasoning, perceptual speed and memory clusters, scholastic aptitude, written language (Aram & Ekelman, 1988), reading, language or verbal learning (Aram, Gillespie, & Yamashita, 1990; Eden et al., 1993; Leavell & Lewandowski, 1990), and arithmetic processing (Ashcraft, Yamashita, & Aram, 1992). It is hypothesized that, as a result of genetic or epigenetic hormonal and/or immunological factors, the cortical language areas are disturbed in their development through migration disorders and abnormal asymmetry, such that normal left hemisphere dominance does not develop, resulting in dyslexia in some children (Njiokiktjien, 1994).

Right hemisphere dysfunction has also been associated with specific learning disabilities. Damage to the right hemisphere in adults is associated with deficits in social skills, prosody, spatial orientation, problem-solving, recognition of nonverbal cues (Semrud-Clikeman & Hynd, 1991), impaired comprehension and production of affective signals, and higher-order cognition about social behaviors (Voeller, 1995). The right hemisphere is therefore implicated in the processing of social-emotional information in the same way that the left hemisphere is specialized for language (Voeller, 1995).

The association of chronic social difficulties coupled with deficits in producing and comprehending emotional expressions, in combination with left-hemibody signs, has been reported as the right hemisphere deficit syndrome (Voeller, 1995). Lower reading performance has also been associated with the right hemisphere (Aram & Ekelman, 1988; Aram et al., 1990; Branch, Cohen, & Hynd, 1995), as have mathematical problems (Ashcraft et al., 1992; Branch et al., 1995; Rourke & Conway, 1997; Shalev, Manor, Amir, Wertman-Elad, & Gross-Tsur, 1995), and visuospatial deficits (Tranel et al., 1987).

With regard to arithmetic disabilities, both the right and left hemispheres have been implicated (Ashcraft et al, 1992; Branch, Cohen, & Hynd, 1995; Rourke & Conway, 1997; Shalev et al., 1995). In the child, early damage or dysfunction in the right or left hemispheres has been reported to disrupt arithmetic learning, with very profound effects resulting from early right hemisphere insults, whereas in the adult, left hemisphere lesions predominate in the clinico-pathological analysis of acalculia or computation difficulty (Rourke & Conway, 1997).

The effective treatment of any condition or disease must be based on an adequate understanding of the etiology and genesis of that condition. Appreciating the neurobiological basis can facilitate the development of effective educational programs, with instructional goals, content, and pace of delivery designed to maximize success for individuals with learning disabilities. However, public policy makers have been slow to recognize the implications of this fact for the field of learning disabilities.

Recognition of the neurobiological basis of learning disabilities does not necessarily lead to a bleak outlook, because the individual's environment has the potential to reduce or amplify the impact of the learning disabilities. Supportive care giving (Kopp, 1990), quality of the home environment (Kalmar, 1996), and socioeconomic factors (Drillien, Thomson, & Burgoyne, 1980; Werner, 1990), as well as educational programs designed specifically to meet the needs of individuals with learning disabilities (Fiedorowicz & Trites, 1991; Lerner, 1989), have the power to mitigate the academic and cognitive deficits associated with the condition.

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Chapter 2

FOCUSING ON MATHEMATICAL DISABILITIES: A SEARCH FOR DEFINITION, CLASSIFICATION AND ASSESSMENT

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ABSTRACT

Although the prevalence of mathematical disabilities seems as high as the prevalence of reading disabilities, research interest for mathematical disabilities was very limited until now (Mazzocco and Myers, 2003; WHO, 1992). Moreover, many theoretical as well as pragmatic issues concerning mathematical disabilities still are unclear. A fundamental stumbling block is the discussion on defining a mathematical disability, or even a learning disability in general. A general search in the literature and practice shows a proliferation in the terminology used. Several authors used different terms for a deficit in mathematical problem solving, such as dyscalculia, acalculia, mathematical disabilities, mathematics learning difficulties, mathematics learning problems, mathematics learning disorders, mathematics learning disabilitiy, mathematics learning retardation, mathematics learning deficiency, … (Desoete, Roeyers and De Clercq, 2004). By giving an overview of the leading definitions and terminology for mathematical disabilities, we want to contribute to a better adjustment of criteria used in future research. By putting terms together, we want to reduce the confusion of tongues in this field.

A second source of contention we want to approach concerns the construction and stability of subtypes for mathematical disabilities. Many authors (e.g. Geary, 2004) made a classification based on their observations and research findings. Since there is no single definition and no single explanation for the cause of mathematical disabilities, researchers classified the syndromes they met in practice from different perspectives. This in turn led to different classifications of the wide range of observations in children with mathematical problems. In this chapter, we also want to give an overview of different typologies.

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Finally we briefly focus on the assessment of mathematical disabilities. Most practitioners make a diagnosis based on observational measures and criterion-based tests. Those tests evaluate whether or not the age-appropriate goals for mathematical education are reached. However, a good assessment of a mathematical disability has to provide children, school, parents and practitioners with a solid base for remediation. We present the TEDI-MATH (Grégoire, Noël and Van Nieuwenhoven, 2003), a diagnostic battery that was recently developed. In contrast to the criterion-based tests, this test results in a profile of the strengths and weaknesses of the child, providing practitioners with a more solid base for remediation.

INTRODUCTION

Most practitioners and researchers currently experience that the incidence of children and adults with mathematical disabilities is not exceptional. Recent research findings demonstrate that the prevalence rate for mathematical disabilities is as high as the prevalence of other well-known and well-studied disorders such as reading disorders and ADHD (Shalev, Auerbach, Manor, and Gross-Tsur, 2000; WHO, 1992). Although the prevalence of mathematical disabilities is high, the research focus on the domain of this disorder still remains limited (Desoete, Roeyers and De Clercq, 2004; Gersten and Chard, 1999; Ginsburg, 1997; Mazzocco and Myers, 2003, WHO, 1992). Nowadays a slight advance in research interest is noticed (Butterworth, 1999).

Consequently there is not yet a unified theory that describes the causes or processes underlying the development of problems with mathematics. The lack of knowledge raises serious questions. In line with Hamill (1990) we think that a clear and accurate idea of the nature of the disability is needed in order to identify, diagnose, prescribe treatment for, teach or remediate, motivate, or generally improve the life of a person who has mathematical disabilities. Scientific research should therefore focus on the current stumbling blocks for definition, criteria, taxonomy and assessment. By giving an overview of the current research findings for those issues, we want to provide a framework for future research and clinical practice in the field of mathematical disabilities.

DEFINING LEARNING AND MATHEMATICAL DISABILITIES

A brief overview of the literature shows a great variety in the terminology and definitions used to describe children with mathematical disabilities (Desoete et al., 2004; Kavale and Forness, 2000). One of the core problems that originate this debate is the lack of scientific evidence on the sense and explanation of learning disabilities (Doris, 1993). As since Kirk (1962) postulated the first definition on learning disabilities, learning disabilities include a broad and varied category of impairments. In his definition, Kirk opens the scope by stating that learning disabilities can originate in cerebral dysfunction as well as in emotional or behavioural disturbances. He includes that the difficulties are not the effect of mental retardation, sensory deprivation or cultural and instructional factors. Furthermore, learning disabilities are expressed as difficulties in the processes of speech, language, reading, writing or arithmetic (Kirk, 1962). A distortion of the basic processes that are essential in learning is

central but the definition does not mention the origin of this problems. This obscurity impedes a good conceptualisation of the domain of learning disabilities.

Since then, a variety of definitions concerning learning disabilities appears. This broad diversity leads to the situation that the definition or the diagnostic tool that is used, determines if a child has a learning disability or not (e.g. Mazzocco and Myers, 2003). These findings have important implications for theory, research and clinical work. First of all a consensus in defining learning and mathematical disabilities is necessary to make a right comparison between researches possible. Further, this definition has to be implemented in assessment tools so that those different instruments can lead clinicians to a same clinical group. Mazzocco and Myers (2003) examined whether children moved in and out of the learning disability categories and stressed the importance of consistent defining criteria.

In the nineties, Hammill (1990) states that a consensus between the most important American researchers on a definition for learning disabilities is near. He analyses 11 definitions postulated by the main researchers and organisations in the field of learning disabilities. In conclusion, he sees the definition of the National Joint Committee on Learning Disabilities (NJCLD) as a powerful candidate for an integrating definition. Hammill (1990) states that this definition is the best one that is available and he argues that it has a high level of acceptance among American organisations. The definition covers a broad range of disorders including the field of listening, speaking, reading, writing, reasoning and mathematics.

> Learning disabilities is a general term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are intrinsic to the individual and presumed to be due to central nervous system dysfunction. Even though a learning disorder may occur concomitantly with other handicapping conditions (e.g., sensory impairment, mental retardation, social and emotional disturbance) or environmental influences (e.g., cultural differences, insufficient/inappropriate instruction, psychogenic factors), it is not the direct result of those conditions or influences (Hammill, Leigh, McNutt and Larsen, 1987, p.109).

Besides the more theoretical definitions, different classifications try to provide more pragmatic definitions for the classification of disorders. While the ICF (WHO, 2001) provides a terminological framework for the different aspects of human functioning, the ICD-10 (WHO, 1992) and the DSM-IV (APA, 2000) are classification indexes for disabilities. The ICD-10 (WHO, 1992) is the taxonomy for mental disorders provided by the World Health Organisation, a specified agency of the United Nations. On the other hand, the Diagnostic and statistical manual of mental disorders (DSM-IV; APA, 2000) is the official American nomenclature based on extensive scientific foundation. Yet, the classification system is of great importance for research and clinical practice all over the world. We here first look at learning processes from an ICF-view and then discuss the criteria for learning disabilities as proposed by the two main nomenclatures.

The International Classification of Functioning, Disability and Health (ICF; WHO, 2001) is a classification system for human functioning and its associated disabilities provided by the World Health Organisation. The classification system was set up in order to reach some consensus in the terminology that is used. The most important functions that are described

concerning learning processes are the mental functions that are related to language (b167) and mental functions related to mathematics (b172).

The International Statistical Classification of Diseases and Health Related Problems (ICD-10, WHO, 1992) on its turn gives an extensive overview of disabilities related to human functioning, including characteristic features and defining criteria. In the ICD-10, five main criteria are set up for learning disabilities in general (WHO, 1992). First of all there must be a clinically significant degree of impairment in the specified scholastic skill. This means that the disabilities are severe and occur only in less than 3% of schoolchildren. The problems are not a part of the normal development and remediation does not lead to direct improvements. Secondly the problems are not originated in mental retardation or impairments in general intelligence. The child's level of attainment must be very substantially below that expected for a child of the same mental age. Furthermore, the ICD-10 stipulates that the difficulties are part of a developmental course. Problem onset must be early in the development of the child. Fourth, the impairments can not be contributed to external factors that could provide sufficient evidence for scholastic failure. The fifth and last criterion states that the developmental disorders of scholastic skills are not directly due to uncorrected visual or hearing impairments. The ICD-10 warns that a distinction between primary and secondary learning disabilities must be made. Since secondary disabilities are due to other (neurological) impairments, only the primary type belongs to the core learning disorders (WHO, 1992).

The diagnostic and statistical manual of mental disorders (DSM-IV) uses similar criteria, although different emphases are made (APA, 2000). First of all, the achievement on a standardised test in scholar skills must be substantially below that expected for age, schooling and general level of intelligence. The disabilities have to cause serious interferences in academic achievements or daily living. Furthermore, there must be a discrepancy, commonly operationalised as a significant discrepancy between achievement and general intelligence. The DSM-IV (APA, 2000) proposes a discrepancy of at least two standard deviations between IQ and the scholastic skills. Only if associated disorders are present, a smaller discrepancy can be assumed. Finally, the disabilities are not directly due to sensory deficits and exceed the consequences of other impairments in the child or the environment (APA, 2000).

The development and description of various existing definitions for learning disabilities and an overview on different operational definitions is given by Kavale and Forness (2000).

Criteria In Defining Learning Disabilities

Taking those definitions together, three main criteria in defining learning disabilities can be distinguished, the discrepancy criterion, the exclusion criterion and the resistance criterion. We discuss those criteria in relation to the definitions proposed above and give some broader comments on the application of those criteria.

The first criterion that is currently used is the discrepancy criterion. This criterion stipulates that a diagnosis of a learning disability only is justified when a great discrepancy between scholastic achievement and general performance or intellectual ability is seen. Whereas the NJCLD (Hammill, 1990) does not mention this condition for the diagnosis of learning disabilities, both the ICD-10 (WHO, 1992) and the DSM-IV (APA, 2000) put forward this condition. This sort of criterion is often used in legislative classifications as

prerequisite for refund of treatment. Although the discrepancy criterion is used a lot in research and clinical practice, the criterion is very unclear. The problem is that a lot of variation exists in the interpretation of the discrepancy. Questions that can be raised are how big the discrepancy has to be and how general performance can be operationalised.

In line with the DSM-IV (APA, 2000), some researchers stipulate that the extent of the discrepancy has to be at least as big as two standard deviations between the chronological grade of the child and the level of achievement that is reached (e.g. Klauer, 1992).

Other authors do not agree with that criterion and have replaced it by a grade equivalent of two years lag between general achievement and the level of scholar skills (e.g. Gross-Tsur, Manor, and Shalev, 1996; Reynolds, 1984; Semrund-Clikeman et al., 1992). However it still remains questionable if any of those criteria is useful for clinical practice since they cannot be used for both younger children and older individuals for whom a discrepancy of two years is not meaningful (Shalev et al., 2000). In Belgium practitioners use a discrepancy of two years in children in grade four or older, mathematical disabilities in younger children are diagnosed when a discrepancy of one year is met (Desoete et al., 2004). On its turn, the ICD-10 classification (WHO, 1992) stays out of the debate by not mentioning a specific discrepancy for learning disabilities. They simply state that the scholar achievement has to be substantially below the expected achievement related to age, schooling and general level of intelligence, but they do not give any criteria of what this really means (WHO, 1992).

A second question that rises concerning the discrepancy model is how the discrepancy can be operationalised. Most of the times an IQ-assessment serves as an indicator for the general level of achievement. Researchers like Gross-Tsur and colleagues (1996) have put forward this operationalisation in their studies. However, this base of an IQ- achievement discrepancy is strongly debated. Siegel (1989) disputes the usefulness of IQ-measurement to detect learning disabilities and argues that many children with low IQ-scores can read at an age-appropriate level. Brody and Mills (1997) argue that children with generally high intellectual capacities but average scores for some learning domains will be seen as learning disabled because of the discrepancy between the two scores. In that case some children classified as learning disabled from the view of the discrepancy criterion may qualify for help even tough their learning skills are in the normal range (Brody and Mills, 1997). On the other hand, some children with learning disabilities with below average intellectual capacities will miss the help they need (Shalev et al., 2000).The DSM-IV criteria (APA, 2000) take this possibility into account by stating that the discrepancy can be smaller in the case that children experience other impairments.

In the debate about the usefulness of IQ-measurement in the assessment of learning disabilities, Siegel (1989) points out that there are no differences in the basic cognitive processes among children of different IQ levels so clinicians could better spent their time in detecting more relevant factors. She even goes further and means that there is not even a logical or empirical ground for involving IQ-scores in the definition of learning disabilities. Siegel (1989) means that the discrepancy model has lead to a great number of children with learning disabilities that are not detected. In line with those findings, Mazzocco and Myers (2003) more recently state that the criterion is not sensitive enough to identify all children with mathematical disabilities. A child with a discrepancy between his IQ-score and his math achievement may have a mathematical disability, but many children with a mathematical disability may not meet this discrepancy-criterion.

In contrast to the previous researchers, Naglieri and Reardon (1993) argue that a discrepancy between intelligence and scholar abilities is a useful measure to detect learning disabilities. They argue that the problem in the debate on the relevance of IQ is the assumption that one can rely on an intelligence score as measured by an IQ-test to determine the intelligence. When using a test battery based on a more comprehensive cognitive processing model, intelligence seems to be relevant to the identification of learning disabilities.

Recent studies found a correlation of .50 between mathematical abilities and intelligence as measured with the WISC-III. Moreover, the correlation of mathematical school achievement with verbal intelligence seems to be higher than with non-verbal intelligence. Kort and colleagues (2002) studied the relation between IQ (as measured with the WISC-III) and mathematical achievement and found correlations of .53 between mathematical achievement and TIQ, .48 between mathematical achievement and VIQ and .45 between mathematical achievement and PIQ.

Returning to the search for current definitions and criteria for learning disabilities, another criterion we encounter is the severeness criterion. We see this criterion however as a variant on the discrepancy criterion we just discussed. The severeness criterion contains that the achievement on scholastic skills is not within the normal range. The ICD-10 criteria (WHO, 1992) explicitly mention the criterion and say that there must be a clinically significant degree of impairment in the specified scholastic skill. Disabilities have to occur only in less than 3% of schoolchildren (WHO, 1992). An exclusion of children based on a distribution of achievement scores in se equalizes the use of a discrepancy as defining factor. We find the criterion in the studies of Kosc (1974) who studied children with mathematical disabilities by classifying all children who scored below the 10^{th} percentile of his assessment instruments as having dyscalculia. Recent studies however still use the criterion (e.g. Geary, 2004; Lewis, Hitch and Walker, 1994). Geary uses the cut-off criterion of the 25^{th} percentile but warrants that only children who have scores across successive academic years beneath this cut-off may have a diagnosis of mathematical disabilities.

A criterion for learning disabilities that is represented in the definition of the NJCLD, ICD-10 and the DSM-IV is the exclusion criterion. The NJCLD originates learning disabilities to a central nervous dysfunction (Hammill, 1990). Since the nomenclatures of the WHO and APA are not based on one single theoretical point of view, they do not mention a cause for the disabilities but also exclude a number of causal conditions (APA, 2000; WHO, 1992). We can group the mentioned exclusion conditions in handicapping conditions in the situation of the child (e.g. sensory impairments, mental retardation or impairments in general intelligence, social or emotional disturbances, …) and external factors (e.g. insufficient or inappropriate instruction, cultural differences, psychogenic factors, …). The ICD-10 makes a distinction between primary and secondary learning disorders based on those causes (WHO, 1992).

A third and last criterion that can be found in definitions for learning disabilities is the resistance criterion. Authors who defend this criterion argue that core learning disabilities only can be diagnosed after a period of remediation is offered. The ICD-10 (WHO, 1992) under scribes this criterion by stating that remediation does not lead to direct improvements. In the DSM-IV we only retrieve that learning disabilities may persist in adulthood, but a resistance criterion is not mentioned.

Defining Mathematical Disabilities

It is clear that a lot of variation exist in the definitions used for the general category of learning disabilities. This of course has influence on the definitions for the different variations of mathematical disabilities.

It was Henschen who first described mathematical disabilities in 1919. He therefore used the term 'Akalkulia'. The term acalculia is still used frequently and most of the times it is used when mathematical disabilities are acquired after brain damage. Denburg and Tranel (2003) define acalculia as

> …an acquired neuropsychological condition in which patients with preciously normal calculation abilities develop impairments in processing numbers as a consequence of acquired brain dysfunction (Denburg and Tranel, 2003, p. 162).

Acalculia can be caused by damage in different brain regions of both hemispheres. In this review, we will not thorough focus on the acquired forms of mathematical disabilities, we refer the interested reader to the chapter of Denburg and Tranel (2003) for a recent overview of the literature on acalculia.

In contrast to the acquired acalculia, difficulties in the domain of mathematical knowledge that arise within a developmental process are most of the time labelled as *dyscalculia* (Njiokikitjien, 2004; von Aster, Deloche, Dellatolas and Meier, 1997). Some authors however use this term for acquired forms of mathematical disabilities (Cornoldi and Lucangeli, 2004; Geary, 2004). Besides this, a proliferation of other terms also is used in the description of dyscalculia. Some authors stress the developmental aspect of this category of impairments by using the term *developmental dyscalculia* (Shalev et al., 2000; Kosc, 1974; Klauer, 1992; Gross-Tsur et al., 1996). Other authors prefer the term *mathematical disabilities* (Kulak, 1993; Light and DeFries, 1995), *arithmetic disabilities* (Badian, 1983) or *arithmetic disorders* (Lewis et al., 1994). Commonly, the terms *mathematical difficulties* (Dowker, 2004) and *mathematical problems* are used when mathematical skills are weak but are not within the clinical range or in children with weak intelligence. In the subsequent text, we prefer to use the term mathematical disabilities as this is the currently most used concept.

When looking at the currently used classification systems, different operational definitions for mathematical disabilities are used.

The ICD-10 (WHO, 1992) classifies mathematical disabilities as a specific disorder of arithmetical skills (code F81.2). They state that the disorder involves specific impairments in those arithmetical skills that can not be explained by general mental retardation or inadequate schooling solely. The disorder concerns the mastery of basic computational skills of addition, subtraction, multiplication and division, rather than the more abstract mathematical skills (WHO, 1992). The diagnosis includes developmental acalculia, developmental arithmetical disorder and the developmental Gerstmann syndrome. The ICD-10 (WHO, 1992) makes a distinction between the specific disorder of arithmetical skills and the acquired arithmetical disorder acalculia. This disorder is classified as a separate disorder. Even so, arithmetical difficulties that are related to reading or spelling disorders or that are attributed to inadequate teaching, are excluded from this category (WHO, 1992).

The ICF (WHO, 2001) defines this function as mental functions related to arithmetic (code b172). This includes specific mental functions related to the determination, the

approach and manipulation of mathematical symbols and processes. The ICF (WHO, 2001) makes the distinction between two sort of functions. The first category contains mental functions related to simple arithmetic (code b1720). Those are specific mental functions related to arithmetic with numbers, like addition, subtraction, multiplication and division. Besides functions for simple arithmetic, the ICF (WHO, 2001) discerns mental functions related to complex arithmetic (code b1721). These functions are associated to complex operations with numbers as the translation of problems that are formulated in language or in mathematical formulas to arithmetical procedures.

The DSM-IV (APA, 2000) finally uses the category mathematics disorder (code 315.1). The essential features are a mathematical ability (as measured by individually administered standardized tests of mathematical calculation or reasoning) that falls substantially below that expected for the individual's chronological age, measured intelligence, and age-appropriate education (criterion A). There has to be a significant disturbance of academic achievement or situations in daily live that require mathematical skills (criterion B). Finally, the DSM-IV (APA, 2000) uses the exclusion criterion by stating that the disabilities can not be explained by any sensory deficit (criterion C, APA, 2000).

PREVALENCE OF MATHEMATICAL DISABILITIES

It is clear that the prevalence of mathematical disabilities will vary depending on the criteria used to define those disabilities (Dowker, 2004; Mazzocco and Myers, 2003). But even while the search for a consensus on criteria and definitions still goes on, and researchers still use a great variety of inclusion conditions, reported prevalence rates are very similar. Geary (2004) finds that between 5% and 8% of school-age children have some form of mathematical disabilities. These figures are confirmed in different countries by several researchers: Badian (1983) finds a prevalence of 6.4% in an American study, the Belgian study of Desoete and colleagues (Desoete, Roeyers and De Clercq, 2004) reports between 3% and 8%. Kosc (1974) finds 6.4% in Bratislava and English studies report prevalence rates of 3.6% (Lewis et al., 1994). German researchers find prevalence between 4.4% (Klauer, 1992) and 6.6% (Haüber, 1995; Hein, 1999), Israeli researchers report 6.5% of children with mathematical disabilities in their country (Gross-Tsur et al., 1996) and von Aster and colleagues find 4.7% in Swiss (von Aster et al. 1997). Nonetheless those similar findings in current research, the DSM-IV (APA, 2000) still estimates the prevalence of mathematical disabilities on 1% of school-age children.

The gender ratio for boys and girls in mathematical disabilities is another point of discussion. Badian (1983) finds boys to have 2.5 times more mathematical disabilities than girls. The universal gender effect that is found in the development of mathematical abilities is highly variable between different countries (von Aster, 2000). This difference has decreased over the last decades (Husen, 1967; International Association for the Evaluation of Education Achievement (IEA), 1996; von Aster, 2000) what indicates that it is not likely to be explained by biologic factors. In contrast with the disproportion in gender ratio found for learning disabilities in general (male-female 3:1; APA, 2000), research of the last decade finds an almost similar prevalence in boys and girls (Haüber, 1995; Hein, 1999, Lewis et al., 1994), with boys doing slightly better (Gross-Tsur et al., 1996 (1:1.1), Klauer, 1992, von Aster,

2000). These little gender difference possibly can be explained by features of the educational setting or educational methods, or differences in attitudes, self-esteem and specific anxieties since they influence the development of motivation and self-directed learning (von Aster, 2000).

It is clear that not all children with mathematical disabilities exhibit the same difficulties. Individual assessment still remains necessary in order to detect all children with mathematical disabilities. A good description of the possible and minimal features of mathematical disabilities will be very useful. In the next section, we focus on different profiles within those disabilities.

SUBTYPES IN MATHEMATICAL DISABILITIES

We use mathematical operations in every day life. Still doing maths is a complex neuropsychological operation. Every operation involves a lot of basic mathematical skills (Shalev and Gross-Tsur, 2001). First of all, we need to have a perfect command of our numbers and the number system we use. We need to know the difference between digits, teens and hundreds. Once we know the system, we can learn operations like summation, addition, multiplication and division. The more complex the calculations become, the more we make an appeal to our short term memory for the retention of intermediate solutions and to remember the different steps of the mathematical procedures we use (Koontz and Berch, 1996). Besides, visuospatial abilities and the construction of mental representations are needed for a good comprehension of the number system (e.g. a mental number line can support our number knowledge) and the calculation of complex procedures. Finally, the long term memory has an important function in speeding up the execution of mathematical calculations since we store basic knowledge in our semantic memory (Shalev, 2004).

Many authors tried to build theoretical models of mathematical functioning. McCloskey and his colleagues (McCloskey, Caramazza and Basili, 1985; McCloskey and Macaruso, 1995) propose a neurocognitive model of mathematical abilities with three main components: number comprehension, number production and the comprehension and application of mathematical concepts. Dehaene (Dehaene, 1992; Dehaene and Cohen, 1991; Dehaene, Spelke, Pinel, Stanescu and Tsivkin, 1999; Dehaene et al., 1996) proposes a triple code model based on a verbal and visuospatial network, existing of verbal, visual and quantity representations. This model is criticized by Campbell and Clark (1988) and as a reaction they formulate the encoding complex theory. Besides those different models, different research findings could discern other neurologic and neurocognitive structures that are important in mathematics (Burbaud et al., 1995; Rickard et al., 2000; Stanescu-Cosson et al., 2000; Van Harskamp and Cipolotti, 2001). Most theories mainly originate in observations of dissociations in various aspects of number processing and calculation in adult subjects with brain trauma. Based on the components of the distinct models, many researchers try to make a classification of distinct profiles in mathematical disabilities since an outburst of every of those mentioned operations is possible. The broad variety of involved skills in doing mathematics makes that we encounter an even larger spectrum of possible disabilities, based on the genetic or attained failure in one or a combination of several distinct basic mathematical skills. Many researchers address to make a classification of those different

combinations and describe several subtypes in learning disabilities (Fuchs and Fuchs, 2002; Knopik, Alarcón and Defries, 1997; Korhonen, 1991; Kronenberger and Dunn, 2003; Padget, 1998). Without searching for a unifying theory on mathematical disabilities, we present an overview of different current or historically important classifications of mathematical disabilities.

In general four subtypes of mathematical disabilities are currently found in scientific research: the subtypes based on procedural deficits, semantic memory deficits, visuospatial deficits and number knowledge deficits. We first describe the general concept of the subtype and then give an overview of the research findings for each pattern and the different terminology used to describe this profile. We will conclude with some critical remarks concerning subtypes in mathematical disabilities.

Procedural Deficits

A first subtype concerns a pattern of impairments in arithmetic procedures. Children (or adults) with this type of mathematical disability make a lot of mistakes in the use of arithmetic procedures and have difficulties in keeping track of the order of different steps in complex calculations. Mathematical performance is characterised by a time-lag in arithmetic procedures and we frequently see the use of algorithms that are normally used by younger children.

This kind of subtype is already described in 1961 by Hécaen, Angelergues and Huillier. In an attempt to find a classification for acalculia, those researchers analyse calculation into component processes and relate clusters of characteristic errors to particular cortical regions. The tripartite Hécaen and his colleagues propose, remains very useful since many researchers still refer to their classification. Hécaen and colleages (1961) describe this pattern as anarithmetria. With this term, they refer to an inability to carry out arithmetic procedures despite intact visual-spatial and number reading skills. The cause of these impairments is attributed to posterior left or bilateral lesions.

Kosc (1974) affirms the existence of this kind of deficits. He distinguishes six subtypes of developmental dyscalculia under which the operational dyscalculia. In his definition, it is an inability to carry out the arithmetic operations.

Badian on his turn describes spatial dyscalculia (Badian, 1983). The planning and execution of complex arithmetical problems often is supported by a visual imaginative faculty. Children with spatial dyscalculia make more errors in the sequence of different steps in the solution of those problems because they exhibit problems with this visual imaginative faculty or with dysfunctions in mental rotation. According to Njiokiktjien (2004), this type of mathematical disabilities can be seen as a subtype of the operational dyscalulia described by Kosc. This profile of problems can nevertheless, according to us, also be classified as a visuospatial form of mathematical disabilities (see further). This confirms the relativity of subclassifications in mathematical disabilities because in practice different typologies are mixed up most of the time.

Von Aster (2000) designs a comprehensive model of developmental dyscalculia, based on his own empirical research and the theoretical work of Anderson (1992), Dehaene (1992), Fodor (1983) and Karmiloff-Smith (1992). He describes a verbal subtype of developmental dyscalculia that can be related to the profile described above. Children who met the criteria

for this sort of dyscalculia had difficulties with the use of counting procedures and routines. By that, they experience difficulties in mental calculations and throughout development, they maintain to use immature strategies. von Aster (2000) describes also difficulties in retrieval strategies and number-fact knowledge in this children. As counting procedures remain immature, those children make many mistakes and thus can not build up a memory for valid number facts. As a consequence, the development of retrieval strategies and number-fact knowledge is delayed. From this theoretical view, there are many connections with the semantic memory subtype that we will describe in the next section.

Another description of procedural deficits in mathematical disabilities can be recognized in the research findings of Cornoldi and his colleagues (Cornoldi, Lucangeli and Bellina, 2002; Cornoldi and Lucangeli, 2004). They propose a diagnostic tree for the assessment of different learning disabilities build up in a theoretical based five level approach (Cornoldi and Lucangeli 2004). Whereas level five takes individual subtyping into account, the authors provide categories of impairments on the fourth level. They describe the procedural deficits subtype as mentioned here as a subtype of mathematical disabilities where deficits in the use of procedures in written calculation are the core problem (Cornoldi and Lucangeli, 2004; Cornoldi et al., 2002).

Recently, Geary (2004) presented a model for subtyping mathematical disabilities based on the cognitive theory and experimental methods. The features of the procedural subtype he describes all consist of difficulties in the execution of arithmetic procedures. Those children exhibit difficulties in sequencing the multiple steps in complex procedures and make a lot of errors in executing them. As the delay hypothesis postulates, these children relatively frequent use procedures that are developmentally too young for their (mental) age. In sum, they have a poor understanding of the concepts they use for the procedures. Where Hécaen and colleagues (1961) attribute the procedural deficits to posterior left or bilateral lesions, Geary (2004) suggests that this kind of subtype may be attributed to a left hemispheric of prefrontal dysfunction.

Semantic Memory Deficits

Besides the procedural subtype, a second pattern of impairments in mathematical disabilities is described as a semantic memory subtype. Generally, arithmetic facts are not automatized, so simple arithmetic problems have to be calculated. This in turn makes that much time is needed in order to give an answer. Sometimes people are able to retrieve numerical facts in the long term memory after all. This however involves a great chance for not giving a correct solution. Because of those different patterns (retrieval from long term memory and/or calculation), reaction times are very unstable and can vary from very quick to uttermost slowly. The PET-studies of Dehaene and colleagues (1996) show that those deficits may be localised in the left basal ganglia. However, neither Hécaen and colleagues (1961) nor Kosc (1974) describe a similar pattern of learning disabilities in their typology.

In a series of studies, Rourke (Fisk and Rourke, 1979; Rourke, 1989, 1993, 1995; Rourke and Conway, 1997; Rourke and Finlayson, 1978; Rourke and Fuerst, 1995; Strang and Rourke, 1983) describes a subtype of learning disability that reflects similar impairments as the semantic memory subtype mentioned here. They describe two distinct profiles that constitute of strengths and weaknesses. The R-S profile includes difficulties in the semantic-

acoustic aspect of the linguistic domain. The difficulties experienced in arithmetic are rooted in verbal deficits due to left hemisphere impairments. In contrast to the other profile (NLD, see further), which constitutes of nonverbal impairments, the R-S children have normal performance on visual, spatial, organizational, psychomotor, tactual and perceptual tasks.

As mentioned earlier, von Aster (2000) described semantic memory problems in the verbal subtype of developmental dyscalculia. Based on a theoretical framework, he originates the acquisition of number-fact knowledge and retrieval strategies in the repeated use of good counting and arithmetic procedures. Children with these kind of mathematical disabilities can not find number fact knowledge accurately so they are delayed in executing procedures. From this point of view, difficulties with number fact knowledge and procedural deficits are closely related so a distinction between the semantic memory and procedural subtype is no longer useful (von Aster, 2000).

However, research evidence for a distinct subtype in semantic memory deficits still was found by Cornoldi and his colleagues (Cornoldi et al., 2002). They describe disabilities in mental and automatized calculation. This specific subtype is expressed in a lower accuracy of mental calculation, slower speed of mental and written calculation, lower enumeration speed and difficulties with retrieving numerical facts (Cornoldi and Lucangeli, 2004).

The model of Geary (2004) also distinguishes a separate subtype for semantic memory deficits. Those children have difficulties in retrieving mathematical facts. If children retrieve the answer, reaction times are very irregular and the error rate is high. Geary (2004) adds that the retrieval errors often are associated with the numbers in the problems, suggesting that the wrong associations are made. This profile of disabilities could be associated with left hemispheric dysfunctions although it is possible that the basal ganglia are involved too (Geary, 2004).

The problem of retrieving elementary arithmetical facts quickly is described by Njiokiktjien (2004) as verbal dyscalculia. He describes children who experience difficulties in language comprehension and passive vocabulary. They can not name figures, symbols, numbers and quantities or they have difficulties with assignments that are presented orally. Although the core deficits of those children are not mathematical, those dysfunctions are expressed in several problems in the field of doing mathematics. Children with verbal dyscalculia have difficulties with conceptual knowledge assignments. Njiokiktjien (2004) argues that those children are very slow in mathematics because they have problems with internal speech (which should be necessary for a quick execution of a lot of operations) and they have difficulties with memorisation and recall of mathematical facts because of their bad verbal memory.

Visuospatial Deficits

A third pattern of mathematical disabilities that is often described in literature contains a conjunction of visuospatial disabilities in the arithmetic domain. This subtype is characterized by problems with insight in and notions of space. Those deficits are typically translated in difficulties in situating numbers on the number line, shuffling numbers in big figures and difficulties in the understanding of geometry (Shalev, 2004).

According to the research findings of Hécaen and colleagues (1961) this type of disabilities is related to posterior right-hemisphere dysfunction. The consequences of those

dysfunctions vary from difficulties in maintaining the decimal place and misalignment of digits in columns to inversions, reversals and even visual neglect. Although the emphasis is slightly different, a similar pattern can be found in the work of Kosc (1974). He describes practognostic dyscalculia as a disturbance in estimating and comparing quantities, enumerating groups of objects and setting out objects in order according to magnitude. Njiokiktjien (2004) adds that this kind of dyscalculia is seen most of the times in combination with severe disorders of speech and language and deficits in performal intelligence. A lot of the children with practognostic dyscalculia suffer also of dyspraxia, which interferes with important skills in the development of elementary calculating (e.g. like finger counting). This of course can be seen as difficulties with abstraction. Those children still remain thinking in a concrete operational way. Njiokiktjien (2004) also describes a separate profile of problems in symbol recognition. He groups this kind of dysfunctions as numerical dyssymbolics, which constitutes of several secondary mathematical disabilities as visual agnosia, deficits in reading of symbols (dyslectical form of dyscalculia) or misalignments and misplacements of digits (dyslectical or dysgraphical dyscalculia; Njiokikitjien, 2004).

In the work of Badian (1983) we recognize the spatial dyscalculia as a description of the 'visuospatial variant' of mathematical disabilities. Badian opens the scope in this description and includes also difficulties in the temporal order or planning. Most of the time, solving complex arithmetical problems requires a good visual imaginative faculty. Distortions of this capacity lead to difficulties in the execution of arithmetical procedures and can therefore also been classified as a procedural problem (Badian, 1983). The twofold classification of this problem in doing mathematics only stresses again the relativity of subclassifications.

In contrast to the R-S profile as mentioned above, Rourke and colleagues (Fisk and Rourke, 1979; Rourke, 1989, 1993, 1995; Rourke and Conway, 1997; Rourke and Finlayson, 1978; Rourke and Fuerst, 1995; Strang and Rourke, 1983) also described a learning subtype originated in a right hemisphere dysfunction. The nonverbal learning disorder (NLD) is characterized by impairments in visual, spatial, organisational, psychomotor and tactual-perceptual skills. The achievement in arithmetic is limited by nonverbal deficits. Rourke (Rourke and Conway, 1997) adds that those children especially have difficulties with novel and complex tasks. However right hemispheric dysfunctions seem to appear frequently, the scientific literature is divided concerning the extensive description of the NLD-profiles of Rourke (Little, 1993; Ruijssenaars, 2001; von Aster, 1994; 2000) and mathematical disabilities where not consistently found in NLD (Gross-Tsur, Shalev, Manor and Amir, 1995; Klin, Volkmar, Sparrow, Cicchetti and Rourke, 1995; van Luit, Kroesbergen, den Engelsman and van den Berg, 2003). Bzufka, Hein and Neumärker (2000) reported evidence for similar right hemispheric dysfunctions in subtypes of mathematical disabilities. Cornoldi and colleagues (2002) could not find this kind of deficits but describe a visuospatial learning disability. This disability is circumscribed as a learning disability confined to the learning of nonverbal material with a presence of a discrepancy between verbal and nonverbal IQ scores and a failure in cognitive neuropsychological tests involving visuospatial memory but not affecting verbal memory (Cornoldi, Venneri, Marconato, Molin and Montinaro, 2003).

Visuospatial deficits in mathematical disabilities are also described in the work of von Aster (2000). Besides the verbal subtype mentioned above, he distinguishes an Arabic subtype. This for instance emerges in difficulties in number placement and vertical alignments. Where we make a distinction between visuospatial deficits and number knowledge deficits, von Aster (2000) places those problems under the same counter.

According to his theoretical framework, difficulties with the Arabic number system and visuospatial disabilities are closely connected and originate the same subtype of developmental dyscalculia.

Recently, Geary (2004) included this kind of subtype in his classification model. He describes the visuospatial subtype as a profile with difficulties in spatially representing numerical and other forms of mathematical information and relationships. Children with this kind of problems also frequently misinterpret spatially represented information. The profile is related to right hemispheric dysfunction (Geary, 2004).

Finally, Mazzocco (2001) reports remarkable higher prevalence of the visuospatial subtype in girls with the fragile X-syndrome. Although this research is based on correlational findings and thus does not provide evidence for the subtyping question, it further founds a possible cognitive and perhaps neurological distinctive pattern for those subtypes.

Number Knowledge Deficits

A less well described profile in mathematical disabilities concerns the subtype with number knowledge deficits. People with this sort of mathematical disabilities miss the insight in the structure of our number system and do not know the specific positions for units, tens and hundreds. Those disabilities often emerge in number reading, number writing, number production and number knowledge.

The first type of acalculia described by Hécaen and colleagues (1961) corresponds to a similar phenotype. It approaches the description of the number knowledge deficits in mathematical disabilities we described, but we still have to be careful when comparing models based on adult mathematical problem solving or patient data to a developmental disorder in children.

Hécaen and colleagues (1961) describe that the patient is unable to read or write the numbers required for successful calculation. This ‘aphasic acalclia’ originates in posterior left (and sometimes bilateral) cerebral lesions (Hécaen, 1962). In 1974, Kosc describes six subtypes in developmental dyscalculia. The ideognostic dyscalulia is characterized by an inability to understand mathematical ideas and relations required for mental calculation. Those children still keep thinking in a sensory motor way and do not dispose of the required preliminal arithmetical skills that are needed for more complex mathematics. This description comes near to the number knowledge deficits we described above. However in our eyes, the observations made in three other subtypes of Kosc (1974) are also comparable to our description of number knowledge deficits. The verbal, lexical and graphical dyscalculia are described as difficulties in respectively naming, reading or writing mathematical terms and relations, including the names of numbers, digits and operation symbols (Kosc, 1974). In contrast to the ideognostic dyscalculia, a form of ‘central dyscalculia’, those types of dyscalculia however can be seen as secondary forms of mathematical disabilities since they are caused by other impairments (respectively in naming, reading or writing).

Njiokikitjien (2004) adopts this profile of difficulties with abstract number comprehension and abstract comprehension of elementary operations, but he describes it as ideognostic dyscalculia, a form of central dyscalculia.

The existence of this kind of subtype is confirmed by the findings of Cornoldi and his colleagues (Cornoldi and Lucangeli, 2004; Cornoldi et al., 2002). In their five level approach

they also describe a pattern of impairments in numerical knowledge. Those impairments can be due to difficulties in size comparison, word-number transcoding, number ordening, enumeration or number dictation.

Difficulties in the reading and comprehension of Arabic numbers are reported by von Aster (2000) as the Arabic subtype of developmental dyscalculia. These children have difficulties in the comprehension of the Arabic notational system and in transcoding between the different modalities. Another characteristic feature of this kind of mathematical disabilities is the difficulties in the place value system and vertical alignments (von Aster, 2000). This description of course comes close to the visuospatial subtype we described above, von Aster does not make a distinction between those two.

In his research in children with neurofibromatosis, fragile X and Turner syndrome, Mazzocco (2001) reports remarkably higher prevalence of number sense problems in children with Turner syndrome. Again, these findings do not provide direct evidence for the existence of this subtype but it can be a sign that different cognitive and neurological patterns in mathematical disabilities can be found (Mazzocco, 2001).

It is clear that the borders between the different subtypes of mathematical disabilities are very vague. In a sense, the third subtype of von Aster (2000) also could be categorised as a number knowledge deficit. Besides the Arabic subtype of developmental dyscalculia, he describes the pervasive subtype of developmental dyscalculia. von Aster describes this subtype as the combination of the two other profiles, the verbal and the Arabic subtype. The pervasive subtype originates in a defective maturation of the analogue magnitude module. This could be caused by genetic influences or early brain damage. The analogue module normally represents a basic sense of numerosity and encodes the semantics of numbers. A defective maturation however impedes the development of the other different mathematical abilities and causes severe mathematical disabilities (Dehaene et al., 1999; von Aster, 2000). Those descriptions nearly approach the description of number knowledge deficits we first gave.

In Table 1 we give an overview of the different subtypes, the used terminology by different researchers and the distinguishing features as described here. We want to stress that this overview is a pure descriptive one and that it is not based on a unifying theory on mathematical disabilities. For every subtype, we mention the different features as they were described by the different authors, those features however are possible but not conditional characteristics of the described subtypes.

It is clear that the different subtypes in mathematical disabilities can not be seen separately (Njiokikitjien, 2004). The outburst of one mathematical ability will influence the functioning and development of other arithmetical skills. Difficulties in number knowledge or visuospatial problems for instance will slow down calculation procedures, which can have an influence on the memorisation of number facts. Besides, since mathematical disabilities are a developmental disorder, manifestations of the disability are related with age and developmental processes (Shalev and Gross-Tsur, 2001). As a matter of fact the profiles of the children we meet in practice are not that clear and constitute of features of different subtypes described above.

Table 1: Subtypes in mathematical disabilities: description of terminology and distinguishing features

Subtype	Used terminology	Characteristic Features
Procedural deficits	Anaritmetria *(Hécaen, Angelergues and Huillier, 1961)* Operational dyscalculia *(Kosc, 1974)* Spatial dyscalculia *(Badian, 1983)* Verbal developmental dyscalculia *(von Aster, 2000)* Procedural subtype *(Cornoldi and Lucangeli, 2004)* Procedural subtype *Geary (2004)*	Difficulties with procedures in (written) calculation Difficulties in sequencing multiple steps in complex procedures Difficulties in planning or execution of complex arithmetic operations Difficulties in mental calculations Difficulties in routines Use of immature strategies Many mistakes in execution of complex procedures Time-lag in arithmetic procedures Poor understanding of concepts in procedures
Semantic memory deficits	R-S profile *(Rourke, 1995)* Verbal developmental dyscaculia *(von Aster, 2000)* Disabilities in mental and automatized calculation *(Cornoldi et al., 2002)* Semantic memory deficits *(Geary, 2004)* Verbal dyscalculia *(Njiokiktjien, 2004)*	Difficulties in retrieval of numerical facts Disabled acquisition of number-fact knowledge Difficulties in the semantic-acoustic aspect of the linguistic domain Lower accuracy in mental calculation Slower speed of mental and written calculation Irregular reaction times Lower enumeration speed for figures, symbols, numbers and quantities High error rate Wrong associations in retrieval Difficulties in conceptual knowledge assignments Difficulties in language comprehension Difficulties with passive vocabulary Difficulties with orally presented assignments
Visuospatial deficits	Visuospatial deficits *(Hécaen et al., 1961)* Practognostic dyscalculia *(Kosc, 1974)* Spatial dyscalculia *(Badian, 1983)* part of Numerical dyssymbolics *(Njiokiktjien, 2004)* Nonverbal learning disorder *(Rourke, 1995)* Visuospatial learning disability *(Lucangeli and Bellina, 2002)* Arabic dyscalculia *(von Aster, 2000)* Visuospatial subtype *(Geary, 2004)*	Difficulties in situating numbers on a number line Disturbance in setting out objects in order according to magnitude Inversions and reversals in numbers Misalignment and misplacements of digits Problems in symbol recognition Disturbance in visuospatial memory Difficulties in understanding geometry Misinterpretation of spatially represented information Nonverbal deficits Problems with insight in and notions of space Difficulties with abstraction Disturbance in visual imaginative faculty Disturbance in enumerating groups of objects Disturbance in estimating and comparing quantities Difficulties in the temporal order or planning Difficulties with novel and complex tasks Visual neglect Eventually dyspraxia

Table 1. (cont.)

Number knowledge deficits	Aphasic acalculia *(Hécaen et al. 1961)* Verbal dyscalculia, Lexical dyscalculia and Graphical dyscalculia, Ideognostic dyscalculia *(Kosc, 1974)* Ideognostic dyscalculia *(Njiokiktjien, 2004)* Difficulties in number knowledge *(Cornoldi et al., 2004)* Arabic dyscalculia, Pervasive dyscalculia *(von Aster, 2000)*	Difficulties in comprehension of Arabic notational system, mathematical ideas and relations Difficulties with abstract number comprehension Disturbance in number knowledge Disturbances in basic sense of numerosity Disturbance of encoding the semantics of numbers Difficulties in transcoding between the different modalities Disturbance in number reading Disturbance in number writing Disturbance in number production Difficulties in size comparison Difficulties in number ordening Difficulties in enumeration Difficulties in number dictation

In sum, many arithmetical topics are not yet studied and the models for the development of mathematical knowledge are not yet finished so the profiles of the different subtypes still could be refined in the light of that knowledge (Geary, 2004). We need to be careful since we here described classifications for developmental mathematical disabilities based on findings in acquired forms (acalculia) or research findings in adults.

Landerl, Bevan and Butterworth (2004) advise that we first need to search for the causes of mathematical disabilities before a good classification can be made. They originate developmental dyscalculia in deficits that are present since birth. Those children can not subitize when they are babies and have difficulties in the comparison of big quantities. When they become toddlers, they do not develop a mental number line and have difficulties in counting (Landerl et al., 2004). Further research in this area is needed since a good comprehension of different patterns in mathematical disabilities can help to find strengths and weaknesses (Njiokikitjien, 2004). Another important and still questioned issue is the stability of the different subtypes of mathematical disabilities. Ginsburg (1997) points out that perhaps some children even can outgrow some mathematics learning disabilities and grow into others. A good remediation of those disabilities will need a solid assessment of the mathematical disability and the detection of possible comorbid diagnose.

CO-MORBIDITY IN MATHEMATICAL DISABILITIES

Although Shalev (2004) reports that mathematical disabilities in general appear as isolated and specific learning disabilities, mathematical disabilities are also common in many other neurological or psychological disabilities (Shalev et al., 2000). We here give a brief overview of different neurologic and developmental disabilities that were reported in association with mathematical disabilities.

Other Learning Disabilities

First of all, high correlations between mathematical disabilities and other learning disabilities are reported. Several authors describe mathematical disabilities as a component of a more generalized learning disabilities including problems with reading, writing and mathematics (Fleishner, 1994; Geary, 1990).

Mathematical disabilities often are associated with poor reading (Badian, 1983; Donlan and Hutt, 1991; Geary and Hoard, 2001). An indication for learning disabilities in primary school could be an early language disorder. Many children with learning disabilities appeared to have developmental language disorders (DLD) when they are toddler. Shalev and colleagues report high comorbidity between developmental language delay and mathematical disabilities as well in kindergarten as in elementary school (Manor, Shalev, Joseph and Gross-Tsur, 2000; Shalev, 1998; Shalev et al., 2000). In a group of 61 children with developmental language delay, 55 percent reach criteria for mathematical disabilities. They suggest that the link between the two disorders may be found in impaired linguistic skills underlying both mathematical disabilities and developmental language delay.

The prevalence of a general mathematics and reading disability varies from 17% (Gross-Tsur et al., 1996) to 43% (Badian, 1983). Kulak (1993) argues that the several similarities in the development of arithmetical and reading skills are responsible for the high co occurrence of both disorders and that the disabilities in both domains will have an influence on each other. Based on their research with twins, Light and DeFries (1995) argue that both environmental as genetic influences are responsible for the high comorbidity.

Besides the high comorbidity between reading and mathematical disabilities, Shalev, Manor, and Gross-Tsur (1997) found that children with mathematical disabilities in combination with reading disabilities are more profoundly impaired than children with mathematical disabilities alone or those with mathematical disabilities and ADHD.

Another disorder that is often reported in children with mathematical disabilities is a writing disability. The prevalence of combined mathematics and writing disabilities is about 50% (Ostad, 1998). In addition, the chronicity of the disability is found to be associated with the severity of disability, the lower IQ, inattention and writing problems (Shalev, Manor and Gross-Tsur, 2005).

Attention Deficit Hyperactivity Disorder (ADHD)

Although the consequences of ADHD often are similar to the consequences of mathematical disabilities or learning disabilities in general, it definitely are different disabilities. This distinction also is expressed in the defining criteria for mathematical disabilities (Kavale and Forness, 2000). However, both disorders are closely related. In 26% of the children with mathematical disabilities comorbid symptoms of ADHD are found (Gross-Tsur et al., 1996) and over 20% of boys with ADHD have mathematical disabilities. (Faraone, Biederman, Lehman, Spencer et al., 1993; Manor et al., 2001).

Children with ADHD have an impaired recall, make careless errors and have inattention for details, thus making numerous mistakes in arithmetic (Lindsay, Tomazic, Levine and Accardo, 1999). Because they work hasty and slovenly they make many procedural mistakes, similar to the use of immature counting strategies (von Aster, 2000). This makes that they

cannot develop solid number fact knowledge through which they develop an impulsive and hasty working style which may contribute to faulty counting (von Aster, 2000).

Several studies try to explain the high comorbidity between mathematical disabilities and ADHD. Faraone, Biederman, Lehman, Keenan and colleagues (1993) studied this co occurrence in boys and found evidence for non-random mating between parents with ADHD and parents with mathematical disabilities. A study with a female population however could not replicate those findings (Doyle, Faraone, DuPre and Biederman, 2001). Based on their findings, they suggest the existence of a separate familial subtype for ADHD with inclusion of a learning disability, but their findings did not reach significance.

Monuteaux, Faraone, Herzig, Navsaria and Biederman (2005) found no evidence for cosegregation or assertive mating between mathematical disabilities and ADHD. These results reinforce the current nosological approach that ADHD and mathematical disabilities are separate categories. They are etiologically distinct and are independently transmitted in families, so separate identification and treatment strategies for children with both disabilities still remain important (Monuteaux et al., 2005). Based on his findings, von Aster (2000) sees a good prognosis if ADHD is the only comorbid disability. An early diagnosis and treatment however is very important. In line with the defining criteria of mathematical disabilities, ADHD should be treated first before giving the diagnosis of mathematical disabilities and starting up remediation (Shalev, 2004).

Social, Emotional and Behavioural Disturbances

Co occurrences between mathematical and emotional, social or behaviour disturbances are frequently reported. Because of the small number of studies, it is difficult to differentiate between mathematical disabilities and other learning disabilities in this domain. For that reason, we here give an overview of the literature on general learning disabilities and specify where possible for mathematical disabilities.

Children with learning disabilities exhibit more social problems than children without those disabilities (Greenham, 1999; Shalev et al, 2005). The high occurrence of social difficulties in children with learning disabilities even led to discussions about the insertion of those problems into the definition of learning disabilities (Hammil, 1990; Kavale and Forness, 2000). Several studies found children with learning disabilities to be more rejected and to be less popular than children of the same age (Greenham, 1999; Kavale and Forness, 1996; Nabuzoka and Smith, 1993; Stanford and Hynd, 1994). Based on teacher information, 80 percent of the children with learning disabilities have problems with social interactions (Kavale and Forness, 1996). Meta-analysis of studies on peer information confirms rejection of 80 percent of children with learning disabilities by peers. 70 percent of them are not seen as a friend (Kavale and Forness, 1996).

Different researchers found children with learning disabilities to have a lower social status than children without learning disability (Kavale and Forness, 1996; Nabuzoka and Smith, 1993). In contrast to children without learning disabilities, those children tend to be more shy (33,3% versus 7%), they need to seek more for help (36,1% versus 11,9%) and they are more a victim of bullying (33,3% versus 7,7%). This in turn is associated with rejection by peers (Nabuzoka and Smith, 1993).

Tsanasis, Fuerst and Rourke (1997) found children with learning disabilities to be less socially competent than their peers. This could be explained by worse academic results, poor social perception, insufficient utilisation of social knowledge and defective role taking behaviour (Greenham, 1999). Dyson (2003) compared social competence of children with learning disabilities and those of their siblings and found them to be weaker. Kavale and Forness (1996) argue that in general, almost 75 percent of children with learning disabilities can be differentiated of children without learning disabilities based on their social skills.

However, many children with mathematical disabilities do not foster psychosocial problems (Rourke and Fuerst, 1991). Greenham (1999) found 40 to 70 percent to be accepted by their peers as children without learning disabilities. It is clear that many research findings in this area contradict each other. This often is due to the use of different definitions and methodological issues (Gadeyne, Ghesquière and Ongena, 2004). Gadeyne and colleagues however could discriminate between children with and without learning disabilities based on a set of psychosocial variables (Gadeyne et al., 2004). They found that the type of learning disability and the defining criteria used, influence the predictions that can be made. The most important predictor in mathematical disabilities they found was poor motivation for learning (Gadeyne et al., 2004).

Comorbidity between mathematical disabilities and behaviour problems also seems to be high. Schachter, Pless and Bruck (1991) estimate that 43 percent of the children with mathematical disabilities have behaviour problems too. Shalev, Manor, Auerbach and Gross-Tsur (1998) found that the prevalence of those behavioural and emotional problems even was higher for children with persistent mathematical disabilities. An excess of social problems was found as well in children with persistent as in children with non-persistent mathematical disabilities. There appears to be a direct correlation between the behavioural phenomena and the mathematical disabilities in the sense that children, who initially had a more profound disability in mathematics, manifest more severe behavioural dysfunctions than children who suffer non persistent mathematical disabilities (Shalev et al., 1998). Psychosocial problems do not increase when getting older, but older children tend to have more conduct disorder and somatic complaints (Tsanasis et al., 1997).

Schachter and colleagues (1991) found significant age differences concerning the psychosocial functioning of children with mathematical disabilities. Children with mathematical disabilities tend to have more internalised problems (Osman, 2000; Prior, Smart, Sanson and Oberklaid, 1999; Rourke and Fuerst, 1992; Shalev, Auerbach and Gross-Tsur, 1995; Tsatsanis et al., 1997). Between 24% and 52% of children with learning disabilities have clinical scores for social, emotional or behavioural disabilities. When looking at children with serious emotional problems, Rock, Fessler and Church (1997) found learning disabilities or severe learning problems in 38% to 75 % of them.

Shalev and colleagues (1995) found that children with mathematical disabilities do not foster a greater chance in having severe depressions than normal population. They statistically do not exhibit more fears than children without mathematical disabilities. Only in subgroups of children with ADHD and comorbid mathematical disabilities, Shalev and colleagues (1995) found higher levels of anxiety. Several studies further found differences in self esteem (Bear and Minke, 1996; Cosden and McNamara, 1997; Priel and Leshem, 1992; Stiehr Smith and Nagle, 1995). Children with learning disabilities tend to have lower academic self esteem than their peers without learning disabilities, but those differences can not be found in other domains (Donceel and Ghesquière, 1998; Greenham, 1999). Greenham (1999) also reports a

higher risk for substance abuse in adolescents with learning disabilities in comparison to their non disabled peers.

Nonverbal Learning Disorder (NLD), Developmental Gerstmann Syndrome and other Neurologic Disabilities

Although some authors describe NLD (Nonverbal Learning Disorder) as a subtype of mathematical disabilities, others see dyscalculia as a characteristic feature of the NLD-syndrome. Njiokitjien (2004) states that mathematical disabilities are one of the minimal symptoms that have to emerge in order to speak of NLD. From that point of view, NLD can not be seen as a comorbid disability of mathematical disabilities, since mathematical disabilities are in itself a feature of the NLD-profile (Ruijssenaars, van Luit, van Lieshout, 2004). The debate about the existence and the features of NLD yet still goes on (Gross-Tsur et al., 1995; Klin et al., 1995; Little, 1993; von Aster, 1994; 2000).

A syndrome that is closely related to the described NLD features and in which mathematical disabilities are frequently reported, is the Gerstmann Syndrome. In the thirties, Gerstmann described adult patients with left hemisphere lesions in the area of the gyrus angularis (Mayer et al., 1999). He found four main deficits in the behaviour of his patients: acalculia, bilateral finger agnosia, left/right disorientation and dysgraphia. Gerstmann found the four symptoms to appear together as the Gerstmann syndrome (von Aster, 2000). Kinsbourne (1968) however reports the same four deficits in children without demonstrated brain lesions and proposes a developmental Gerstmann syndrome. Since then, many researchers have questioned the existence of the constellation as a true clinical syndrome (Benson and Geschwind, 1970; Grigsby, Kemper and Hagermann, 1987; Miura et al., 1994; PeBenito, 1987; Poeck and Orgass, 1975; Shalev and Gross-Tsur, 1993; Slade and Russel, 1971; Spellacy and Peter, 1978; von Aster, 1993). The four deficits have also been reported as isolated problems and different combinations of two or tree features were found. Kinsbourne even describes constructional dyspraxia as a fifth symptome that should be part of the syndrome (Kinsbourne, 1968; Kinsbourne and Warrington, 1963). Although the NLD syndrome is related to a specific type of mathematical disabilities, Rourke and Conway (1997) report no specific arithmetical deficits in the Gerstmann syndrome. Although it still remains controversial, the developmental Gerstmann syndrome seems to be identified more than originally was thought and appears to have some heuristic value (Rourke and Conway, 1997; Suresh and Sebastian, 2000).

Mathematical disabilities also are reported in relation to the Fragile X-syndrome since they frequently have been associated with the developmental Gerstmann Syndrome (Grigsby et al., 1987; Rourke and Conway, 1997). Further, mathematical disabilities are reported in combination with Turner Syndrome (Mazzocco, 2001), the Shprintzen syndrome (Eliez et al., 2001), phenylketonuria (PKU) or neurofibromatosis type 1 (NF1; Mazzocco, 2001), Klinefelter syndrome or disease of Duchenne (Njiokiktjien, 2004). Seidenberg and colleagues (Seidenberg et al., 1986) found an increased prevalence of mathematical disabilities in children with epilepsy.

ASSESSMENT OF MATHEMATICAL DISABILITIES

It is clear that the manifestation of mathematical disabilities is different in every child. In Table 1 we give an overview of the main characteristics of the different subtypes in mathematical disabilities. In clinical practice however, these categories are not that delimited at all. The phenotypes we mostly encounter are combinations of features out of different subtypes. Taking this into account makes the diagnostic process of course difficult. In their research in diagnostic criteria, Mazzocco and Myers (2003) concluded that the number of children with mathematical disability varied in function of the definition for mathematical disability and/or the diagnostic tool they used. Besides the need for a consensus in defining mathematical disabilities, these findings implicate that clinicians and researchers have to be carefully in selecting an appropriate assessment since different assessment tools lead to a different clinical group.

Nowadays, a lot of diagnostic tools are designed to diagnose mathematical disabilities (see also Denburg and Tranel, 2003; Mazzocco and Myers, 2003; Njiokikitjien, 2004; Shalev, 2004; Shalev and Gros-Tsur, 2001; von Aster, 2000). The mainstream of those tests are addressed to assess the performance of specific arithmetical abilities. In Belgium for instance, practitioners often use the KRT-R and TTR. The Revised Kortrijk Arithmetic test (Kortrijkse Rekentest Revision, KRT-R; Centrum voor Ambulante Revalidatie, 2005) is a 60-item Belgian mathematics test on domain-specific knowledge and skills, resulting in a percentile on mental computation, number system knowledge and a total percentile. The psychometric value of the KRT (with norms January and June) has been demonstrated on a sample of 3,246 children. A standardized total percentile based on national norms can be used. Another diagnostic tool that is used a lot in Belgium is the Arithmetic Number Facts test (Tempo Test Rekenen, TTR; de Vos, 1992). This is a test consisting of 200 arithmetic number fact problems (e.g., 5 x 9 =_). Children have to solve as many number-fact problems as possible out of 200 in 5 minutes. The test has been standardized for Flanders on 10,059 children (Ghesquière and Ruijssenaars, 1994).

The use of this kind of tests in assessing children with mathematical disabilities has been found not to be reliable. Desoete and her colleagues investigated if they could identify all children with mathematical disabilities with the aid of those tools and found that only the combination of several diagnostic instruments could prevent that the diagnosis was determined by the choice of test (Desoete et al., 2004). In spite of those findings, the use of those performance-based tests still remains popular in clinical practice. This can partly be explained by the great diversity of test materials that are available but an even more important reason could be the fact that refundation for remediation still is determined by discrepancy- and criterion-based definitions. The variability reflected in Table 1 however provides support for not relying on a fixed test battery. Practitioners have to consider the appropriateness of individual measures and their combination to identify the problems of children with mathematical disabilities (Kamphaus, Petosky and Rowe, 2000; Mazzocco and Myers, 2003). We need tests based on a validated model of the specific learning process we are assessing. Not many such tests are recently available. There are some instruments (Butterworth, 2003, Von Aster, 2002) that can provide a first screening of the child's learning problem. However, screeners do not give us a sound foundation for remediation. There is also the Key Math Revised (Connoly, 1988). Although designed with care the Key Math Revised has no support

by a validated theoretical model of mathematics learning and no explanation is proposed for understanding the errors children make. An instrument that is validated by a combination of theoretical models and therefore can be used for an in-depth diagnostic assessment seems to be the TEDI-MATH (Van Nieuwenhoven, Grégoire and Noël, 2001). This multicomponential instrument is based on a combination of neuropsychological (developmental) models of number processing and calculation. It has an age range form 4 to 8 years of age (kindergarten to 3rd grade) and has already been translated into a German, Dutch and French version. It was standardized on a sample of 550 Dutch speaking Belgian children from the beginning of the 2nd grade of the nursery school to the end of the 3rd grade of primary school. The test enlightens five facets of arithmetical and numerical knowledge: logical knowledge, counting, representation of numerosity, knowledge of the numerical system and computation. Table 2 shows the subtests of the TEDI-MATH and some examples of test items.

Twelve basic scores can be computed. The reliability coefficients vary from .70 (for computation with pictures) to .99 (for transcoding). A validation study showed that the TEDI-MATH could discriminate among pupils with different levels of mathematical knowledge according to the teachers. The raw scores of the TEDI-MATH are converted into percentiles. It is suggested to pay attention to scores under pc 25 and to consider possible disabilities under pc 10. However the authors state that these cut off scores are only indications and should be used with great caution. The diagnosis of learning disability can only be drawn from a global assessment of the child, including learning, intelligence, emotions, family and school context. In sum, it is important to distinguish delay of deficits and to consider consistency in performance – both at a point in time and over time. (Mazzocco and Myers, 2003). Since mathematical capacities are dynamic, there is much variability in the developmental process (Shalev, 2004). The individual profile of strengths and weaknesses can shift over time as a function of the growth process. This makes a one-time assessment unreliable (Mazzocco and Myers, 2003).

Table 2: Subtests and examples of test-items of the TEDI-MATH

Subtest	Content and example of item
1.Knowledge of the number-word sequence	- Counting as far as possible - Counting forward to an upper bound *(e.g. "up to 9")* - Counting forward from a lower bound *(e.g. "from 7")* - Counting forward from a lower bound to an upper bound *(e.g. "from 4 up to 8")* - Count backward - Count by step *(by 2 and by 10)*
2.Counting sets of items	- Counting linear pattern of items- Counting random pattern of items - Counting a heterogeneous set of items - Understanding of the cardinal
3. Knowledge of the numerical system	3.1. Arab numerical system *- Judge if a written symbol is a number* *- Which of two written numbers is the larger*
	3.2.Oral numerical system *- Judge if a word is a number* *- Judge if a number word is syntactically correct* *- Which of two numbers is the larger*

Table 2. (cont.)

	3.3. Base-ten system *- Representation of numbers with sticks* *- Representation of numbers with coins* *- Recognition of hundreds, tens and units in written numbers*
	3.4. Transcoding *- Write in Arab code a dictated number* *- Read a number written in Arab code*
4. Logical operations on numbers	4.1. Seriation of numbers *Sort the cards form the one with fewer trees to the one with the most trees*
	4.2. Classification of numbers *Make groups with the cards that go together*
	4.3.Conservation of numbers *e.g.: Do you have more counters than me? Do I have more counters than you?* *Or do we have the same number of counters? Why?*
	4.4. Inclusion of numbers *e.g.: You put 6 counters in the envelope. Are there enough counters inside the envelope if you want to take out 8 of them? Why?*
	4.5. Additive decomposition of numbers *e.g.: A shepherd had 6 sheep. He put 4 sheep in the first prairie, and 2 in the other one. In what other way could he put his sheep in the two prairies?*
5. Arithmetical operations	5.1. Presented on pictures *e.g.: There are 2 red balloons and 3 blue balloons. How many balloons are there in all?*
	5.2. Presented in arithmetical format - Addition *(e.g.: "6+3"; "5+..=9", "..+3=6")* - Subtraction *(e.g.: "9-5", "9-…=1", "…-2=3")* - Multiplication *(e.g.: "2x4" "10x2")*
	5.3. Presented in verbal format *e.g. "Denis had 2 marbles. He won two others. How many marbles had Denis in all?"*
	5.4. Understanding arithmetical operation properties (conditional knowledge) *e.g.: addition commutativity: "You know that 29+66=95. Would this information help you to compute 66+29? Why?"*
6. Estimation of the size	6.1. Comparison of dot sets (subitising)
	6.2. Estimation of size *Comparison of distance between numbers. E.g.: target number is 5. What number is closer to this (3 or 9)?*

CONCLUSION

A focus on the literature in mathematical disabilities points out that many gaps in this domain still remain. First of all, consensus has to be reached in the search for a theory based definition for mathematical disabilities. Different criteria are nowadays used and it seems that

a valid definition has to be based on the discrepancy as well as the severeness, the exclusion and the resistance criterion. This will enable scientific researchers and practitioners to demarcate the field of mathematical disabilities.

Further, besides the research on brain injury patients and acquired forms of mathematical disabilities, researchers also have to focus on the causes underlying the developmental forms of mathematical disabilities. Conceptual models based on those theoretical insights will help to sort out relevant and irrelevant factors in the development of these disabilities and will help to discern the characteristic features.

In this chapter we proposed four main subtypes in mathematical disabilities: a subtype with procedural deficits, semantic memory deficits, visuospatial deficits and number knowledge deficits. Further research on the different manifestations of mathematical disabilities has to discern the causes of those different patterns. Moreover, we need to investigate whether these subtypes are stable over time and if different remediation is needed. Those insights in turn make that assessment can be tuned to the different profiles of children with mathematical disabilities since comprehensive tests are needed in order to offer a solid remediation based on the strengths and weaknesses of every child.

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Chapter 3

MATHEMATICAL DISABILITIES IN GENETIC SYNDROMES: THE CASE OF VELO-CARDIO-FACIAL SYNDROME

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ABSTRACT

The past decade, there has been much interest in the characterization of the various cognitive processes implicated in the development of Mathematical Disabilities (MD). A valuable contribution to this line of research might be the study of the cognitive phenotype of disorders of a *known* genetic origin with a high prevalence of MD, because the study of these well-defined subgroups may provide a window onto the characteristics of MD in general. Indeed, several cognitive phenotypes of genetic disorders, such as Turner Syndrome, Velo-Cardio-Facial Syndrome and Spina Bifida, include MD.

This chapter extensively reviews the research on mathematical disabilities in children with Velo-Cardio-Facial Syndrome. This genetic condition is known to be the most frequent microdeletion syndrome with an incidence of 1/4000 live births. It will be shown that children with VCFS experience difficulties in mathematics. The research in VCFS on the cognitive correlates associated with MD, such as working memory, will be described as well as the brain imaging studies that point to specific deficits in math related brain areas in these children.

However, the reported studies on MD in VCFS still have some methodological shortcomings, such as the selection of appropriate control groups and the lack of taking into account environmental variables, like instructional environment or socio-economic factors. Additionally, some critical remarks on math assessment in these studies can be

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formulated. These comments may provide some guidelines for future research on MD in genetic syndromes in general and MD in VCFS in particular.

INTRODUCTION

The characterization of the various cognitive processes implicated in the development of mathematical disabilities (MD) is still a major concern among researchers (Butterworth, 2005; Geary, 2004; Ginsburg, 1997). This characterization process encompasses both the delineation of the impairment in the math specific competencies that constitute the math deficit, such as difficulties in retrieving arithmetic facts (e.g. Geary, Hamson & Hoard, 2000; Jordan, Hanich & Kaplan, 2003), as well as general domain-independent cognitive skills that are related to the development of MD, including working memory (e.g. Bull, Johnston & Roy, 1999; McLean & Hitch, 1999; Swanson & Sachse-Lee, 2001), lexical retrieval speed (e.g. Garnett & Fleischner, 1983) and processing speed (e.g. Bull & Johnston, 1997).

A valuable contribution to this study of MD might be the investigation of the cognitive phenotype of disorders of a known genetic origin[2] that have a high prevalence of MD (Cutting & Denckla, 2004; Mazzocco, 2001), because the study of these *well-defined* subgroups of children with a genetic risk for the development of MD may provide a window onto the characteristics of MD in general. Moreover, the study of genetically mediated MD may also allow for developing models of different subtypes of MD (Cutting & Denckla, 2004; Mazzocco, 2001). Finally, studies of genetic disorders are important "case studies" for understanding how neurobiological factors, such as genes and brain development, are related to cognitive processes implicated in MD (e.g. Cutting & Denckla, 2004; Mazzocco, 2001; Scerif & Karmiloff-Smith, 2005).

Mathematical disabilities have been described as one of the core features in several genetic disorders, such as Turner Syndrome (Mazzocco & McCloskey, 2005) and Spina Bifida (Barnes, Smith-Chant & Landry, 2005), and in mental retardation syndromes, such as Fragile X Syndrome (Mazzocco & McCloskey, 2005), Williams Syndrome (Ansari et al., 2003) and Prader-Willi Syndrome (Bertella et al., 2005).

In this chapter, we will focus on another common genetic disorder with a high prevalence of MD, namely Velo-Cardio-Facial Syndrome (VCFS). After a brief description of the clinical characteristics of the syndrome, we will review the research in children with VCFS on MD and its associated cognitive correlates. Additionally, neuroimaging studies in children with VCFS will be described. As this research is in its early stages, it suffers from several methodological limitations, such as control group selection and math assessment issues. These weaknesses will be critically examined in the second part of this chapter, in order to provide possible guidelines for future research on MD in genetic syndromes in general and MD in VCFS in particular.

[2] In the remainder of this chapter, the shorthand of 'genetic disorders' will be used.

VELO-CARDIO-FACIAL SYNDROME

1. Clinical Characteristics

Velo-Cardio-Facial Syndrome or Chromosome 22q11 Deletion Syndrome was firstly described by Shprintzen and colleagues in 1978 (Shprintzen et al., 1978). In the early nineties, it was discovered that VCFS is caused by a submicroscopic deletion in chromosome 22q11, which is detectable with 100% accuracy by means of modern molecular genetic techniques (i.e. Fluorescence *in situ* Hybridisation (FISH)) (Scambler et al., 1992). At present, VCFS is the most frequently known microdeletion syndrome in man with an incidence of 1 in 4000 live births (Scambler, 2000). Although the clinical presentation of VCFS is quite variable, the major clinical characteristics of the syndrome are velopharyngeal abnormalities (mainly velopharyngeal insufficiency) with hypernasal speech, congenital heart anomalies, a typical face with a broad nasal bridge, small mouth and ear abnormalities, and learning disabilities (Cuneo, 2001; Swillen, Vogels, Devriendt & Fryns, 2000). General intellectual abilities of children with VCFS are lower than average (mean IQ about 75) with about 55% of the children scoring into the borderline to normal intellectual range (IQ > 70) and about 45% having (mild) intellectual disability (Swillen et al., 1997). The IQ profile is often characterized by a VIQ-PIQ discrepancy, in favour of the VIQ (Moss et al., 1999; Swillen et al., 1997). Although learning difficulties were initially described as one of the core features of VCFS, only recently the picture of this cognitive phenotype, although still fragmental, is emerging (for a review see Campbell & Swillen, 2005; Zinkstok & Van Amelsfoort, 2005).

2. Cognitive Phenotype

The cognitive phenotype of children with VCFS will be described in three sections. First, we will review research on the psychoeducational profile of children with VCFS. Next, we will provide an overview of the studies on cognitive correlates of MD in VCFS. Finally, brain imaging studies that point to specific deficits in math related brain areas in children with VCFS will be discussed. Appendix 1 lists the available studies on the cognitive phenotype of children with VCFS. As stated above, about 45% of the children with VCFS has mental retardation (Moss et al., 1999; Swillen et al., 1997). Since we are interested in children with specific learning disabilities or primary learning disorders, we will focus in our review of cognitive studies on children with VCFS without mental retardation (i.e. IQ > 70), as the presence of mental retardation generally implies learning difficulties.

2.1 Psychoeducational Profile in Children with VCFS (IQ > 70)

The first major study specifically addressed to examine the psychoeducational profile of children with VCFS was reported by Moss et al. (1999). Sixteen school-aged children (IQ > 70; age range: 6-15 years) completed the Wechsler Individual Achievement Test (WIAT) for reading, spelling and mathematics. Their composite reading and spelling scores were within the average range (group mean z-scores: reading: $z = -0.23$, spelling: $z = -0.21$), whereas scores in math achievement were significantly lower (group mean *z*-score = -0.81). A

further analysis of the subtest scores on the math achievement test indicated that mathematical reasoning and rote calculation skills appeared to be equally impaired. On the reading test, single-word reading and reading comprehension yielded similar results.

These results were further replicated by Swillen et al. (1999). Seven primary school children with VCFS (mean age: 10.5 years) of borderline to normal intelligence (IQ > 70) completed standardized achievement tests in reading, spelling and math. A similar psychoeducational profile emerged: Group mean reading (z = 0.04) and spelling (z = -0.50) scores were within the average range, whereas math achievement was particularly impaired (group mean z-score = -1.43). The sample of Moss et al. was further extended in follow-up studies (Bearden et al., 2001; Wang, Woodin, Kreps-Falk & Moss, 2000; Woodin et al., 2001) and these studies yielded the same psychoeducational profile of preserved reading and spelling skills compared to lower performance in mathematics.

De Smedt, Swillen, Ghesquière, Devriendt, and Fryns (2003) reported that this psychoeducational profile occurred already in preschool children with VCFS of borderline or normal intelligence. These children showed relatively preserved phonological skills, while some of them had already remarkable deficits in counting ability. A more detailed analysis of the test protocols showed that preschool children with VCFS had preserved knowledge of written numbers and (simple) counting, while most of them experienced problems in comparing quantities. The latter indicates that these children may have some impairment in the representation of magnitude or the understanding of the meaning of number (e.g. Robinson, Menchetti & Torgesen, 2002).

It should be noted that the reported studies on achievement only used standardized achievement tests. Recently, Simon, Bearden, McDonald-McGinn and Zackai (2005) examined some aspects of mathematical ability in primary school children with VCFS (mean age: 10.1 years) more into detail. Basic numerical processing was exploratory investigated by means of a dot counting task and a numerical magnitude comparison task in twelve primary school children with VCFS and fifteen typically developing control children. Children with VCFS were significantly slower in dot counting compared to IQ and age-matched controls. A further analysis of the results revealed that children with VCFS were only slower in counting (enumerating numerosities 4-8) but not in subitizing (enumerating numerosities 1-3). A similar impairment in speed of counting dots has also been reported in children with MD (Landerl, Bevan & Butterworth, 2004; see also Hitch & McAuley, 1991). On the magnitude comparison task, children with VCFS made significantly more errors and showed a qualitatively different performance pattern than controls, which suggests an impairment in their representation of magnitude. Such an impairment in representing magnitudes has been described in children with MD by Landerl et al. (2004), although these authors found that, compared to matched controls, children with MD were only significantly slower without making more errors.

In an fMRI study on adolescents with VCFS (mean age: 15.5 years), basic single-digit arithmetic performance was examined using a verification paradigm (Eliez et al., 2001). Eight adolescents with VCFS and eight age and sex matched controls solved two- or three-operand no-carry addition and subtraction problems. Adolescents with VCFS made more errors than controls on the more difficult three-operand problem types, but not on the simple two-operand items. Although adolescents with VCFS performed in general slower compared to controls, no group differences in response times were found.

In sum, borderline to normal intelligent children with VCFS have relatively preserved reading (decoding) and spelling skills while showing significant impairment in mathematics. As such, VCFS might be a useful model to study children with MD without comorbid reading difficulties (often referred to as MD-only). Epidemiological studies on learning disorders (Gross Tsur, Manor & Shalev, 1996; Lewis, Hitch & Walker, 1994) indicate that MD and reading disabilities co-occur frequently. In addition, it has been demonstrated that children with MD without comorbid reading difficulties and children with combined MD and reading disabilities show different performance patterns on both math-related and general cognitive tasks (e.g. Geary et al., 2000; Jordan et al., 2003; Rourke, 1993). Consequently, studies on MD should differentiate between these two groups of children.

2.2 Math Related Cognitive Functions in Velo-Cardio-Facial Syndrome

Research examining the cognitive correlates of MD (e.g. Bull et al., 1999; McLean & Hitch, 1999; Swanson & Sachse-Lee, 2001) has widely established that children with MD have impairment in working memory (i.e. the flexible cognitive system that is engaged in the temporary storage and processing of information (Miyake & Shah, 1999)). The majority of studies examining working memory (WM) in children with MD employs the well known multicomponent model of WM developed by Baddeley and Hitch (Baddeley & Logie, 1999). At the core of this model is the Central Executive (CE) responsible for the control, regulation and monitoring of complex cognitive processes. In addition, this model encompasses two subsidiary systems of limited capacity, that are used for the temporary storage of respectively phonological (i.e. the Phonological Loop) and visual-spatial (i.e. the Visual-Spatial Sketchpad) information. The latter two systems can be considered analogous to the original short-term memory concept, as they are only used for temporary storage. These subsystems are assessed by means of typical short-term memory tasks, such as the recall of digits or locations. CE-ability is generally assessed by tasks requiring both storage and simultaneous processing of information and therefore, such tasks are considered to be typical working memory tasks. Central Executive functioning can be further fractionated into separate but overlapping subprocesses, such as inhibition (i.e. the suppression of dominant action tendencies in favor of more goal-appropriate behavior), shifting (i.e. the ability to shift attention or to shift between strategies or response sets) and updating (i.e. the encoding and evaluation of incoming information for relevance of the task at hand and subsequent revision of information held in memory) (e.g. Baddeley, 1996; Bull & Scerif, 2001).

Taking this into account, we review studies on memory in children with VCFS in two parts. The first part comprises results on short-term memory ability (i.e. Phonological Loop and Visual-Spatial Sketchpad), whereas the second part encompasses studies on working memory and executive functioning (i.e. Central Executive).

2.2.1 Short-Term Memory

Reports on short-term memory skills in VCFS consistently indicate that these children have preserved verbal short-term memory abilities, while performing considerably weaker on tasks comprising visual-spatial short-term memory (Bearden et al., 2001; Lajiness-O'Neill et al., 2005; Sobin et al., 2005; Swillen et al., 1999; Wang et al., 2000; Woodin et al., 2001). For example, Wang et al. (2000) examined short-term memory skills in 35 primary school children with VCFS (mean age: 8.1 years). As a group, children with VCFS performed on

average on verbal short-term memory, as measured through a number recall task, but scored approximately one standard deviation below the standardization sample mean on a spatial memory task. Subsequently, Bearden et al. (2001) assessed 29 children with VCFS (mean age: 10.3 years) using a comprehensive test battery, and compared their performance with published normative data. Children with VCFS had average verbal short-term memory abilities but performed significantly weaker (i.e. more than one standard deviation below the standardization sample mean) on tasks measuring visual-spatial short-term memory. Moreover, within visual-spatial memory, Bearden et al. (2001) observed a significant discrepancy between spatial memory and object memory in favour of object memory. Recently, Lajiness-O'Neill et al. (2005) examined memory performance on the Test of Memory and Learning (TOMAL) of nine children and adolescents with VCFS (mean age: 12.6 years). Sure enough, children with VCFS performed better on verbal than on nonverbal memory tasks. In addition, they performed much lower on the nonverbal memory tasks compared to children with autism and to children of comparable IQ, whereas on the verbal memory tasks, no such differences were found. Finally, in the studies of Woodin et al. (2001) and Sobin et al. (2005), children with VCFS performed significantly better on tests of verbal short-term memory compared to visual-spatial short-term memory, but their group mean score on visual-spatial short-term memory was still within one standard deviation from the standardization sample mean. Thus, whether visual-spatial short-term memory should be considered deficient in children with VCFS remains open to question (see also Stiers et al., 2005).

It is interesting to note that poor performance on visual-spatial short-term memory tasks has also been reported in children with MD (D'Amico & Guarnera, 2005; McLean & Hitch, 1999; van der Sluis, van der Leij & de Jong, 2005), although not all studies are consistent with this (Bull et al., 1999).

2.2.2 Working Memory and Executive Functioning

Three studies have reported preliminary evidence for working memory difficulties in children with VCFS (Lajiness-O'Neill et al., 2005; Sobin et al., 2005; Woodin et al., 2001). Woodin et al. (2001) found that children and adolescents with VCFS (n = 50; mean age: 10.3 years) were particularly impaired on the Trail Making Test, a well-known task to assess the mental shifting aspect of the central executive. Interestingly, children with MD appear to have similar deficits within the same particular task (McLean & Hitch, 1999; Van der Sluis, De Jong & Van der Leij, 2004). In the study of Sobin et al. (2005), children with VCFS (n = 40; mean age: 7.7 years) performed more than one standard deviation below the standardization sample mean on a similar working memory task (Auditory Attention Response Set; this task measures children's ability to maintain selective auditory attention and to shift between sets of stimuli) of the NEPSY Developmental Neuropsychological Battery for Children. Finally, Lajiness-O'Neill et al. (2005) reported that children with VCFS performed weaker on a digit span backward task compared to siblings and children with autism, though this difference only approached conventional levels of statistical significance.

Recently, two independent studies examined executive control in primary school children with VCFS using the Attentional Network Test (Bish, Ferrante, McDonald-McGinn, Zackai & Simon, 2005; Sobin et al., 2004). Both studies revealed that children with VCFS had difficulties in the inhibition of information irrelevant to the task. More specifically, children with VCFS scored significantly weaker on an index measuring the ability to inhibit prepotent

responses in favour of less automatized ones, compared to typically developing children. Comparable deficits in the inhibition of irrelevant information have also been demonstrated in children with low mathematical ability (e.g. Bull & Scerif, 2001).

2.3 Brain Imaging

An extensive review of neuroimaging studies in VCFS has been provided by Zinkstok and van Amelsfoort (2005). Two structural MRI studies have reported a reduced volume of left parietal lobe in children and adolescents with VCFS (Eliez, Schmitt, White & Reiss, 2000; Kates et al., 2001). A more recent diffusion tensor imaging study (i.e. a tool to investigate the white matter tract structure and coherence) reported aberrant (particularly left) parietal white matter tracts in children and young adults with VCFS (Barnea-Goraly et al., 2003). In an exploratory fMRI study by Eliez et al. (2001), adolescents with VCFS demonstrated different brain activation patterns in the posterior left parietal lobe during a single-digit arithmetic task, compared to sex- and age-matched controls. More specifically, aberrant activation was noted in the left supramarginal gyrus. It should be noted that the parcellation of the parietal lobe into different regions, that were related to arithmetic performance, was relatively broad, which made it difficult to find more subtle changes in activation patterns within these areas. Such a fine-grained analysis is warranted as it has been demonstrated that different parts of the parietal lobe relate to different aspects of mathematical cognition (e.g. Dehaene, Piazza, Pinel & Cohen, 2003).

To summarize, the reported studies point to posterior parietal lobe abnormalities in children and adolescents with VCFS. Current (adult) neuro-anatomical models of mathematical cognition emphasize the role of these posterior parietal (and frontal) networks as key brain structures for numerical competence (e.g. Dehaene et al., 2003; Nieder, 2005). Accordingly, the mathematical disabilities described in children with VCFS might correlate with abnormalities in the organization of parietal networks of these children. As research on the neuro-anatomical correlates of mathematical cognition in both typically developing children (e.g. Kawashima et al., 2004; Temple & Posner, 1998) and children with MD (e.g. Isaacs, Edmonds, Lucas & Gadian, 2001) is still in its early stages, such theory remains, however, speculative and will require further validation, preferably by direct experimentation.

2.4 Conclusion

There is converging evidence for a characteristic psychoeducational profile in borderline to normal intelligent children with VCFS, demonstrating relatively preserved reading and spelling skills while having remarkable difficulties in mathematics. At the general cognitive level, there is emergent support for better verbal compared to visual-spatial short-term memory skills and for impairment in working memory and executive functioning in children with VCFS. Finally, neuroimaging research in these children indicates minor abnormalities in left parietal lobe areas known to be involved in mathematical cognition.

Compared to other developmental disorders, it should be noted that within this well-defined group of children with VCFS, there might be considerable variability. In order to account for this heterogeneity between different subjects within a syndrome, research on the cognitive phenotype of a genetic disorder may also benefit from a larger number of detailed case studies (e.g. Stiers et al., 2005). These studies might capture more precisely subtle

deficits that would have been overlooked in the analysis of group average scores. Additionally, it would be advisable that group studies also report observations at the individual level, in order to fully account for intra-syndrome variability or to provide important guidelines for further research. A careful characterization of this variability can even aid studies at the genetic level. For example, two independent studies have recently found an association between the cognitive phenotype and the genetic constitution in VCFS, more specifically a polymorphism of the COMT gene, which is located in the 22q11 deleted area (Baker, Baldeweg, Sivagnanasundaram, Scambler & Skuse, 2005; Bearden et al., 2004). Although the two polymorphisms performed weak in arithmetic, there were differences in working memory between both genotypic variants, but both studies were contradictory with regard to the direction of the difference between the two polymorphisms.

It has been suggested that the reported cognitive phenotype shows similarities to that of children with a "Nonverbal Learning Disability" (NLD) (Bearden et al., 2001; Fuerst, Dool & Rourke, 1995; Moss et al., 1999; Swillen et al., 1999; Woodin et al., 2001). Recent research on cognition in VCFS does not entirely confirm this hypothesis, since not all studies report a deficit in visual-spatial abilities, known to be the hallmark feature of NLD (Laijeness-O'Neill, et al., 2005; Sobin et al., 2005; Stiers et al., 2005). Additionally, brain imaging data in children with VCFS are not consistent with the reported right hemisphere deficit in children with NLD (Rourke & Conway, 1997).

METHODOLOGICAL CONSIDERATIONS IN RESEARCH ON MD IN VCFS

The reported studies on mathematics disabilities and its associated cognitive correlates in VCFS are just a first step to provide a complete understanding of the cognitive and brain systems that support the MD in children with VCFS. From a methodological point of view, these studies still have shortcomings with regard to the selection of appropriate confounding variables (or consequently comparison groups) and to the assessment of the cognitive abilities under study (Einfeld & Hall, 1994; Finegan, 1998; Ginsburg, 1997). These limitations will be described in the next two sections. Besides, it should be noted that the study of genetic disorders generally implies small samples, as these disorders are relatively rare (e.g. compared to learning disabilities in general). Evidently, this affects the statistical power of these studies and therefore, such studies can highly benefit from small sample research strategies, such as the use of multivariate within-subjects designs (e.g. Venter & Maxwell, 1999).

1. Selection of Confounding Variables

In order to find out whether the reported deficits are characteristic features of the VCFS cognitive phenotype (i.e. primary or due to the 22q11 deletion itself as opposed to secondary deficits), potentially confounding variables related to individual differences in MD should be taken into account. This problem should be tackled either by incorporating a control group

matched to the children with VCFS with respect to the confounding variable(s) or by statistically controlling for the confounding variable(s) through the use of covariates.

Up until now, the reported studies examining MD in VCFS only took age and sex into account as confounding variables, except the study by Simon et al. (2005). However, individual differences in mathematics are highly influenced by differences in intellectual ability (e.g. Geary, Hoard & Hamson, 1999; Jordan et al., 2003). Because children with VCFS generally have lower than average intellectual abilities (Moss et al., 1999; Swillen et al., 1997), this should be taken into account in research on MD within this syndrome in order to exclude that the reported difficulties in mathematics are caused by a global intellectual deficit. To date, only Simon et al. (2005) tried to address this problem by incorporating the Processing Speed index, computed from the Wechsler Intelligence Scale for Children, as a control variable in their research design.

Additionally, it is known that environmental variables, such as socioeconomic status (e.g. Jordan, Kaplan & Hanich, 2002) and instructional environment (Geary, Bow-Thomas, Liu & Siegler, 1996; Ginsburg, 1997; Jordan et al., 2002), are highly related to individual differences in math performance. For example, Jordan et al. (2002) found that instructional program (i.e. problem-centered vs. traditional approach) had a differential effect on achievement growth in mathematics. To the best of our knowledge, no empirical research on VCFS has controlled for these variables. In order to minimize as much as possible effects of math instruction, one could select for each child with VCFS a control child from the same class (e.g. Landerl et al., 2004) and match the two children individually on a series of relevant variables, such as sex, age, IQ and socioeconomic status.

2. Assessment of Mathematics

In the reported studies on MD in children with VCFS, the assessment of mathematics is restricted to *general standardized achievement* tests, except the studies by Eliez et al. (2001) and Simon et al. (2005). These measures only yield a general total score, which solely reflects the relative performance averaged across all the assessed mathematical areas. However, such a total score does not provide information on the strengths and weaknesses of children within the broad domain of mathematics. As such, these tests do not pay attention to the multidimensional nature of mathematics. Mathematical ability indeed covers a wide range of subskills and consequently, children can have difficulties in one or several of these subdomains (Geary, 2004; Ginsburg, 1997; Kulak, 1993). Hence, it is not known whether children with VCFS have a differential – and if so, in which subdomain(s) – or general impairment in mathematics. It is therefore necessary for future research to include various carefully delineated mathematical topics that children are attempting to master through primary school (e.g. the comprehension and production of number, counting skills, number facts, multidigit calculation, word problem solving, and the like). Such an approach has been proven a successful starting point for the elucidation of the math deficits of children with MD in general (e.g. Geary et al., 2000; Hanich, Jordan, Kaplan & Dick, 2001). In addition, it is advisable to select those mathematical competencies that are directly related to the teaching of mathematics, which makes it possible to derive guidelines for educational intervention.

In order to provide an in depth understanding of the math related cognitive processes in children with MD, assessment of arithmetic performance may not exclusively be addressed

through accuracy scores. Consequently, more sensitive measures, such as *response times* and *strategy use*, should be considered (Ansari & Karmiloff-Smith, 2002; Ginsburg, 1997; Kulak, 1993). In research on VCFS, only the studies of Simon et al. (2005) and Eliez et al. (2001) administered response times, but it should be noted that similar studies in children with MD are scarce. For example, some studies have documented that children with MD have slower counting rates (Geary & Brown, 1991; Hitch & McAuley, 1991). Hanich et al. (2001) found that children with MD were significantly slower, compared to typically developing children, in solving number fact problems and story problems. Furthermore, children with MD who are good readers were still faster than children with combined MD and reading disabilities on the number fact test. Recently, Landerl et al. (2004) demonstrated that children with MD were significantly slower in low level number processing abilities, such as number comparison and counting. These authors concluded that such impairment may be the hallmark feature of children with MD and suggested that these impairments may have considerable effects on the development of other mathematical abilities (e.g. Robinson et al., 2002). In sum, the analysis of children's response times might be a useful tool to unravel more subtle deficits in children with MD.

Additionally, the analysis of the strategies that children apply during problem solving, has been a successful method to characterize the development of single-digit arithmetic in both typically developing children (for a review see Siegler, 1996) and children with MD (for a review see Geary, 2004). For example, it has been widely documented that children with MD apply the same repertoire of strategies as their normally achieving peers but differ from the latter in the frequency, the accuracy and the speed with which these strategies are executed (e.g. Geary, 2004). Thus, in order to gain a more profound insight in the arithmetic performance of children with VCFS, data with respect to *strategy use* should also be considered (e.g. Ginsburg, 1997; Kulak, 1993). To date, no such research has been carried out in children with VCFS.

CONCLUSION

In this chapter, we have reviewed research on mathematical disabilities and its associated (neuro)cognitive correlates in children with VCFS. From a theoretical point of view, these studies can add to our understanding of the different cognitive processes implicated in the development of MD. Furthermore, the study of such a *well-defined* subgroup of children offers a unique opportunity to study the link between cognition, brain development or neuronal functioning and genes. Although we are still far away from a complete understanding of this complex pattern of interrelationships, current advances in neurological measurement and knowledge of the genome promise progress in the near future.

The study of the cognitive phenotype of genetic disorders has also important clinical and educational implications. As children with VCFS are known to be at risk for the development of MD, they may highly benefit from early intervention or stimulation programs within the area of mathematics (e.g. Griffin, 2003), so potential learning failures can be lessened.

Future studies on MD in VCFS (and other genetic disorders as well) should take into account the multidimensional nature of mathematics in order to fully elucidate the math impairment in this genetic disorder. Through the investigation of a wide range of different

mathematical skills, a profile of strengths and weaknesses might be gradually created. Such a profile may serve as an important guide to develop different remediation strategies, targeting the specific deficits of this syndrome. Furthermore, studies that investigate directly how the psychoeducational profile derives from more general cognitive competencies, such as working memory, are highly needed (Wang et al., 2000). Finally, there is no doubt that future studies on the cognitive phenotype in VCFS should take into account meaningful confounding variables.

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APPENDIX 1

Summary of studies related to mathematics and its cognitive correlates in children with VCFS

Study	VCFS Group N	Age range (years)	IQ data[3]	Comparison group	Measures used[4]
Moss et al. (1999)	16	6 - 15	VIQ = 87 PIQ = 75 TIQ = 80	None, Standardization sample	Reading, Spelling and Mathematics (Wechsler Individual Achievement Test; WIAT)
Swillen et al. (1999)	9	6 - 12 *M* = 10.5	VIQ = 80 PIQ = 73 TIQ = 74	None, Standardization sample	Reading, Spelling, Mathematics Visual Perceptual Skills (Gardner) Visual-Motor Integration (Beery) Visual attention Rey Auditory Verbal Learning Test Tactile Perceptual Skills (Benton) Wisconsin Card Sorting Test
Wang et al. (2000)	35	5 - 12 *M* = 8.1	VIQ = 79 PIQ = 73 TIQ = 74	None, Standardization sample	Reading, Spelling, Mathematics (WIAT) Number Recall (K-ABC) Spatial Memory (K-ABC)
Bearden et al. (2001)	29	*M* = 10.3	VIQ = 81 PIQ = 75 TIQ = 76	None, Standardization sample	Reading and Mathematics (WIAT) Wide Range Assessment of Memory and Learning (WRAML) California Verbal Learning Test Dot Locations (Children's Memory Scale)
Eliez et al. (2001)	8	*M* = 15.5	Not available	Age- and sex-matched controls	Single-digit arithmetic task

[3] IQ data reported always refer to VCFS group means assessed using the Wechsler Scales unless otherwise noted.

[4] Only measures relevant to MD and its cognitive correlates in VCFS are included.

Study	VCFS Group N	Age range (years)	IQ data[3]	Comparison group	Measures used[4]
Woodin et al. (2001)	50	6 – 17 *M* = 10.3	VIQ = 83 PIQ = 73 TIQ = 76	None, Standardization sample	Reading, Spelling and Mathematics (WIAT) WRAML Trail Making Test
De Smedt et al. (2003)	13	5 – 7 *M* = 6.3	VIQ = 93 PIQ = 85 TIQ = 88	None, Standardization sample	Metalinguistic Awareness Counting Skills Reading, Spelling, Math
Sobin et al. (2004)	32	5 – 11 *M* = 7.6	Not available	Sibling controls	Attention Networks Test
Bish et al. (2005)	18	7 - 14 *M* = 9.2	Not available	Typically developing controls	Attention Networks Test (adapted)
Laijeness -O'Neill et al. (2005)	9	*M* = 12.6	VIQ = 77 PIQ = 68 TIQ = 70	Sibling controls Children with autism IQ-matched children	Test of Memory and Learning (TOMAL)
Simon et al. (2005)	12	7 - 14 *M* = 10.1	VIQ = 83 PIQ = 77 TIQ = 78	Sibling controls Typically developing controls	Visual enumeration task Magnitude comparison task Visual attention task
Sobin et al. (2005)	40	5 – 12 *M* = 7.7	Stanford-Binet subtests	None, Standardization sample	Stanford-Binet subtests: Vocabulary, Quantitative Bead Memory, Memory for Sentences NEPSY Developmental Neuropsychological Battery for Children

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Chapter 4

GENERAL HEALTH AND ASSOCIATED BIOCHEMISTRY IN A VISUAL-PERCEPTUAL SUBTYPE OF DYSLEXIA

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ABSTRACT

The general health of adults and juveniles with a visual-perceptual subtype of dyslexia known as Irlen Syndrome (IS) was assessed by a self-administered questionnaire, and the responses were investigated in relation to changes in urinary and plasma biochemistry. The prevalence and severity of a number of the symptoms assessed by self-report for a one-week period showed significant differences when compared to their control peers. Increases in symptoms for the IS subjects indicated possible problems with the dysregulation of the immune system, photophobia, neurocognition, mood and with muscle cramps and twitches. The significant increases in these problems suggested that in IS, reading difficulties were accompanied by reductions in the general "well-being" of the individual. The reported severity of both the IS and the general health symptoms were associated with alterations in the levels of specific plasma lipids and urinary metabolites for the IS cohort. The results suggested that in IS the general health of the individual may be poorer and that these changes, along with the symptoms that define the syndrome, may be associated with anomalous biochemistry. Examination of these associations provides further insight to understanding the aetiology of this learning disability.

INTRODUCTION

The term dyslexia is used to describe a specific difficulty in learning to read and write that does not stem from low general ability, a lack of educational opportunity or the presence of neurological or sensory difficulties including optometric problems. Irlen Syndrome has been described as a visual subtype of dyslexia involving symptoms indicative of the presence of a visual-perceptual dysfunction. The symptoms, which occur during reading for people with Irlen Syndrome, include print distortion, light sensitivity, eyestrain, fatigue and a

reduced span of recognition and are unrelated to any optometric deficiency (Irlen, 1991). These same visual symptoms have also been described in some individuals with dyslexia and found to correlate with signs of essential fatty acid (EFA) deficiency (Richardson et al., 1999). The treatment of these visual-perceptual difficulties with coloured filters has met with much scepticism although it has not been claimed that coloured filters will be of benefit to every individual with a reading difficulty. Coloured filters have been shown to provide significant and ongoing benefits to both adults and children with reading difficulties (Evans and Joseph, 2002; Jeanes et al., 1997; Noble, Orton, Irlen, and Robinson, 2004; Robinson and Conway, 1994) by reportedly improving print clarity and reducing eyestrain allowing reading skills to be gained or improved. The use of colour in reducing visual-perceptual difficulties and improving reading performance was first described by a New Zealand school teacher, Olive Meares, in 1980 (Meares, 1980) and then again in 1983 by Helen Irlen, an American psychologist, who termed this form of dyslexia Scotopic Sensitivity Syndrome (Irlen, 1983). Today, it is more commonly known as Meares-Irlen Syndrome or Irlen Syndrome (IS) although it is also sometimes referred to as visual discomfort (Conlon, Lovegrove, Chekaluk, and Pattison, 1999).

A number of different explanations have been given for the visual-perceptual difficulties seen in IS, and in dyslexia, and also for the mechanism by which coloured filters can alleviate these difficulties. The theories of causation have included an over-sensitivity of the retina/brain to certain light frequencies (Irlen, 1991), a deficit within the magnocellular visual pathway (Stein, 2001) and the presence of biochemical anomalies affecting the visual system such as deficiencies or altered metabolism of EFAs (Horrobin, Glen, and Hudson, 1995). The benefits provided by coloured filters in reducing print distortion and eyestrain, which then allow for reading improvement, may be attributed to an effect on the processing of the magnocellular visual pathway (Chase, Ashourzadeha, Kellya, Monfetteb, and Kinseyc, 2003) or in the case of the retinal sensitivity theory as filtering out certain frequencies of light (Irlen, 1991). However, both the mechanisms by which coloured filters function and the aetiology of IS have yet to be established.

Although defined as a form of reading disability, other problems have been reported to accompany both IS and dyslexia including problems with concentration, memory and poorer motor skills and coordination (see Beaton, 2004; Irlen, 1991). A significantly higher incidence of dyslexia has been reported amongst families with a high schizophrenic proband and individuals with dyslexia often show schizotypal personality traits (Horrobin et al., 1995). In one study, children with IS were shown to be more anxious, neurotic and to have lower self-concepts than a peer group who were also reading disabled but did not report symptoms of IS (Cotton and Evans, 1990). In contrast however, an adult group of subjects with IS did not demonstrate such differences in their personalities (Venable, 2000). A higher incidence of immune and autoimmune disorders has been reported for both individuals with developmental learning disorders (Hugdahl, Synnevag, and Satz, 1990) and their families (Crawford, Kaplan, and Kinsbourne, 1994). Dyslexia and IS both show a high familial incidence (see Beaton, 2004; Robinson, Foreman, and Dear, 1996; Robinson, Foreman, and Dear, 2000) and it has been postulated that genetic factors may predispose an individual to both learning disability and immune disorders although the existence of a genetic link between the immune system and learning disorders has been disputed (Gilger et al., 1998). Dyslexia has been associated with a gene in the major histocompatibility complex (MHC) on chromosome 6. The MHC plays a role in the regulation and functioning of the immune

system. Along with an increased tendency towards atopic conditions an increased prevalence of autoimmune diseases has also been suggested in dyslexia (Crawford et al., 1994; Hugdahl et al., 1990; Pennington, Smith, Kimberling, Green, and Haith, 1987).

Detrimental impacts upon the central nervous system (CNS) resulting from viral infection, or the host's immune response, have also been implicated in the development of behavioural and learning disorders. Diseases of the CNS for example can result from infection of the newborn during birth with the herpes simplex virus (Alter, 2004). Cron (1996) suggested that milder forms of such an infection could result in some learning disorders. It has been suggested that infection of retinal cells by the human herpes virus 6 can impact upon vision by affecting retinal functioning (Arao et al., 1997). A continual activation of the immune system resulting from a chronic viral infection, could also adversely affect visual processing resulting in the print distortions reported in IS (Robinson, McGregor, Roberts, Dunstan, and Butt, 2001). Such changes may also explain the development of dyslexia and IS that can accompany the onset of Chronic Fatigue Syndrome (CFS) (Robinson et al., 2001). Although the causes of CFS are still under investigation CFS has often been reported as following a viral-like illness and the syndrome is often accompanied by symptoms suggestive of a pathogenic challenge such as low level fever, lymphodynia and myalgia (McGregor et al., 2000). Light sensitivity occurs in both CFS (Merry, 1991; Potaznick and Kozol, 1992) and IS and although there are numerous known causes of photophobia its physiology is not well understood (Main, Vlachonikolis, and Dowson, 2000). Photophobia is common amongst people suffering from migraine headache and can occur as result of infections such as meningitis. Headache has also been commonly reported in IS (Irlen, 1991).

Infection occurring in pregnancy has been suggested as causing inflammation within the foetal brain, leading to changes during neuronal development that could then result in the difficulties experienced by individuals with dyslexia (Taylor, 2002). The high familial incidence of dyslexia has been explained as resulting from a genetic predisposition in some individuals towards an increase in the immune system's inflammatory response to infection (Taylor, 2002). Taylor (2002) proposed that the use of polyunsaturated fatty acids (PUFA) in treating learning difficulties might function to reduce an inflammatory response. In a study of the plasma levels of lipids in an IS group of school age students the authors also suggested that changes in the lipid levels seen, including a trend toward lower n-3 and n-6 fatty acid levels, could be attributed to infection and that the host's response to the infection would be under the control of genetic and/or environmental factors (Sparkes, Robinson, Dunstan, and Roberts, 2003).

The role of infection and possibly inflammation in the aetiology of dyslexia, as opposed to a deficiency in PUFAs alone, was supported by an investigation of the plasma lipid levels of a group of juveniles with IS. Although lower mean levels of n-3 and n-6 fatty acids were revealed for the IS group, in comparison to a control group, no significant differences in EFA homeostasis were found (Sparkes et al., 2003). Other changes in lipid levels were revealed however, that could be explained by the presence of a chronic infection. Total cholesterol levels were reduced whilst the odd-carbon length fatty acid heptadecanoic acid (C17:0) was increased for the IS cohort. A reduction in total cholesterol levels can occur during viral infection in response to the production of interferon (Dixon et al., 1984) whilst odd-carbon length fatty acid levels have been found in human cell membranes in the presence of both viral and bacterial infections. In a study of the pathogenesis of meningitis, heptadecanoic acid was found in the erythrocyte membranes of children suffering from viral or bacterial

meningitis but was not detected for the healthy controls (Kramarev, Voloshina, and Bryuzgina, 2001). Whether an increase in odd-carbon length fatty acids in IS could result in a direct change in the structure and function of neuronal membranes and contribute to the visual perceptual difficulties claimed for IS, or that it accompanies other changes occurring in the syndrome, requires further investigation.

The present study aimed to determine whether the general health of people reporting symptoms of IS, but free from other significant medical or psychiatric conditions, would be poorer than that of healthy individuals who did not have IS symptoms. It was further hypothesised that, if present, changes in the health of the IS subjects, and the severity of the four key IS symptoms, would be associated with alterations in metabolic homeostasis as evidenced by changes in the excretion of various urinary metabolites and in the relative abundance of plasma lipids. Alterations in the balance of the relative levels of the excreted metabolites and plasma lipids, associated with changes in symptom severity, may be interpreted as changes occurring in metabolic processes in IS.

METHOD

Subjects

The study group included 25 adults and children (mean age 21.9 yrs) with moderate to severe symptoms of IS and 37 healthy age- and sex-matched asymptomatic controls (mean age 22.5yrs). The study participants were recruited from the general public or were clients of the Special Education Centre, University of Newcastle who had been referred as a result of reading and writing difficulties. Any subjects who reported on interview a previous diagnosis of a significant medical or psychiatric disorder including CFS, depression and anxiety or a behavioural disorder such as Attention Deficit Hyperactivity Disorder (ADHD) were excluded from the study. The subjects ranged in age from 10 years to 45 years and 44% were male. There was no significant difference in the age- and sex-makeup or socio-economic status of the IS and control groups.

Measures

The participants were assessed for symptoms of IS, and their response to coloured filters in alleviating these symptoms if present, using the Scotopic Sensitivity Screening Manual (Irlen, 1992). The manual comprises three sections that include the assessment of an individual's performance on a number of visual tasks and improvement on the visual tasks and in reading ability with the use of the coloured Irlen filters. In the present study four areas, and their improvement with the use of coloured filters, were rated whilst reading and performing the visual tasks. These areas were eyestrain and fatigue; print distortions and clarity; light sensitivity and finally reading speed, accuracy and duration. The validity of the manual has previously been assessed with significant differences shown to exist between those with reading disability and normal readers for all sections of the manual (Robinson, Hopkins, and Davies, 1995; Tyrrell, Holland, Dennis, and Wilkins, 1995).

The general health of the study participants was assessed for a seven-day period using a self-report general health symptom questionnaire containing over 80 items (McGregor et al., 1996a, 1996b). The participants were asked to indicate how much they had been affected by each of the items (ranging from 0 = "not at all" to 4 = "extremely") including indicators of fatigue, infection, allergies, photophobia, headache and chronic pain, negative mood changes, neurocognitive difficulties, musculoskeletal problems and gastrointestinal tract problems.

URINARY METABOLITES AND PLASMA LIPIDS

All subjects were required to collect a first morning urine sample. A 12-hour fasted 10ml blood sample was also collected from each subject in the morning. The samples were processed, extracted and their composition determined using Gas Chromatography/Mass Spectrometry techniques (Dunstan et al., 1999; McGregor et al., 1996a). The relative abundances of over 30 lipids were determined and included polar lipids saponification products, saturated fatty acids, unsaturated fatty acids (incorporating the n-3 and n-6 series) and animal and plant sterols. Amongst the 26 known urinary metabolites that were assessed, were amino acids, organic acids and amines.

STATISTICAL ANALYSIS

The age- and sex- characteristics of the groups were assessed using Student's t-test and ANOVA whilst socio-economic status was analysed using the Mann-Whitney U test. Analysis of the general health questionnaire data was carried out using Chi-square and the Fisher Exact Probability test. The lipid and urinary metabolite data were assessed for normality with the Shapiro Wilks' W test. The percentages of the lipid and urinary metabolite composition were arcsine-transformed before statistical analysis in order to improve normality. Correlation analyses between lipid/metabolite levels and the IS symptoms and general health questionnaire symptoms, which were found to be significantly more severe for the IS group, were carried out using Spearman Rank Order Correlation analysis. All data were processed using Microsoft® Access 2000 (Redmond, WA, USA), Microsoft® Excel 2000 (Redmond, WA, USA) and StatSoft, Inc. STATISTICA (data analysis software system) version 6 (Tulsa, OK, USA).

RESULTS

The sensitivity and specificity of the responses recorded for the general health questionnaire were calculated for the IS and control groups and the findings presented in Table 1. In this particular instance, sensitivity refers to the proportion of IS patients who reported having experienced a difficulty or symptom over the previous week. The specificity of a symptom refers to the percentage of individuals in the control group who did not report the occurrence of that difficulty.

Table 1. Sensitivity and specificity of general health symptoms assessed by questionnaire: comparison of symptom prevalence between control and IS groups

Symptom	Sensitivity (%)	Specificity (%)	p value
General Symptom			
Photophobia	68.0	83.8	<0.0002
Recurrent oral ulceration	32.0	100	<0.0004
Allergies	44.0	89.2	<0.008
Neurocognitive Symptom			
Memory disturbance	80.0	67.6	<0.0003
Forgetfulness	84.0	62.2	<0.0004
Slowness to ensure correctness	68.0	70.3	<0.004
Mind going blank	64.0	73.0	<0.004
Mental confusion	64.0	73.0	<0.004
Trouble concentrating	80.0	51.4	<0.03
Difficulty with words	44.0	83.3	<0.05
Mood Change Symptom			
Repeated unpleasant thoughts	60.0	73.0	<0.01
Nervous when alone	40.0	86.5	<0.04
Musculoskeletal Symptom			
Muscle cramps	32.0	91.9	<0.02
Muscle twitches	36.0	89.2	<0.04

Statistical test = Chi-square test and Fisher Exact Probability test. n = 37 and 25 for control and IS groups respectively. Only statistically significant results presented.

Significant differences in the prevalence of fourteen of the general health symptoms assessed were found for the IS cohort in comparison to the controls. In all cases the symptoms were increased for the IS group suggesting that they were “less well” than their control peers. Difficulties with mood and neurocognition were indicated by the results, with the IS subjects commonly reporting deficits in memory and concentration and an increase in the prevalence of mood symptoms associated with depression or anxiety. Of the symptoms that were of a more physical nature, the IS group reported a higher incidence of muscle cramps and muscle twitches. The changes seen in the health of the IS group also included an increase in the prevalence of symptoms indicative of alterations within the immune system, with sensitivity to light, allergies and mouth ulcers all reportedly more prevalent for the IS group. Light sensitivity is one of the key features of this form of dyslexia and was assessed as part of the diagnostic process. It was no surprise therefore that it was elevated for the IS group. Of particular interest however, was the result obtained for the prevalence of mouth ulcers. Almost one third of the IS cohort reported suffering from recurrent mouth ulcers during the preceding week in comparison to the control group, none of whom reported experiencing a mouth ulcer over the same period. The increased prevalence of allergies and recurrent mouth ulceration suggest that deficits within the immune system may be present in IS.

As recurrent mouth ulceration was the only symptom to produce a specificity of 100% it was decided to determine whether the severity of mouth ulceration would be associated with

other of the general health symptoms assessed for the IS group (Table 2). Correlation analysis revealed that the reported severity of recurrent mouth ulcers was positively associated with a number of symptoms including other symptoms that occur as a result of infection.

Table 2. Significant correlations between reported severity of mouth ulcers over a seven-day period (scale : 0 = "not at all" to 4 = "extremely") and the severity of general health symptoms (self-report) for the IS group

Symptom Severity	Spearman R	p value
General symptoms		
Food cravings	0.58	<0.003
Urgent urination	0.55	<0.005
Fatigue	0.45	<0.03
Avoiding activities due to physical problems	0.42	<0.04
Sciatica	0.40	<0.05
GIT/IBS symptoms		
Diarrhoea	0.48	<0.02
Abdominal pain	0.48	<0.02
Constipation	0.45	<0.03
Infective symptoms		
Sore throat	0.52	<0.009
Sore lymph nodes – neck	0.50	<0.02
Sore lymph nodes – under arms	0.40	<0.05
Sore lymph nodes - groin	0.40	<0.05
Mood change symptoms		
Repeated unpleasant thoughts	0.46	<0.03
Frequent arguments	-0.42	<0.04
Musculoskeletal symptoms		
Pain in joints on movement	0.42	<0.04

Statistical test = Spearman Rank Order Correlation analysis. *n* = 25 for the IS group.

Positive associations were revealed with sore and swollen lymph nodes and also with sore throats indicating that an increase in the severity of the mouth ulcers, reported by the IS subjects, was often accompanied by an increase in the severity of other symptoms commonly seen during an infection. Symptoms indicating an increase in fatigue and depression were also positively correlated with the severity of mouth ulceration, both of which have been associated with infectious illness (Bennett et al., 1998; see Pollak and Yirmiya, 2002). The gastrointestinal problems such as abdominal pain and diarrhoea, as well as the severity of reported joint pain, were all accompanied by an increase in mouth ulceration for the IS group. The only significant negative correlation occurred with the reported "getting into frequent arguments". The result suggests that the more severe the mouth ulceration the less arguments the individual was likely to have and may be explained by an increase in fatigue amongst the IS subjects experiencing mouth ulcers. In combination, the results point to the IS group being in poorer health than their control counterparts and that symptoms commonly associated with

the presence of low-level viral infections were increased in association with recurrent mouth ulceration.

In order to determine whether alterations in metabolic homeostasis would accompany changes in the severity of the four core symptoms of IS, and accompany the changes seen in the health of the IS subjects, correlation analysis was performed. Correlation coefficients for the severity of the general health symptoms, which were significantly more severe for the IS group in comparison to their control peers, and the percentage abundance of urinary metabolites and plasma lipids were determined. Only those results that were found to be different from those of the control group have been retained and are presented in Table 3 and Table 4. The results of correlation analysis for the urinary metabolite percentage abundance data revealed numerous significant associations between the key features of IS and with a number of the general health symptoms.

Table 3. Significant correlations between urinary metabolites (percentage abundance) and core IS symptom severity, symptom improvement with Irlen lens use and with severity of general health questionnaire symptoms within the IS cohort

Reported Symptom	Metabolite	Spearman R	p value
IS Symptom			
Print distortion	3-methylhistidine	0.62	<0.0009
	1-methylhistidine	0.57	<0.004
	lysine	0.40	<0.05
	serine	-0.46	<0.02
	aconitic acid	-0.46	<0.03
	phenylacetic acid	-0.44	<0.03
Print distortion improvement	1-methylhistidine	0.55	<0.005
	3-methylhistidine	0.52	<0.009
	lysine	0.42	<0.04
	phenylalanine	0.42	<0.04
Eyestrain	β-amino-isobutyric acid	-0.41	<0.05
Reading difficulties	3-methylhistidine	0.42	<0.04
	threonine	-0.42	<0.04
	serine	-0.40	<0.05
Reading difficulty improvement	3-methylhistidine	0.42	<0.04
	serine	-0.41	<0.05
General Health Symptom			
General Symptom			
Photophobia	leucine	0.40	<0.05
Allergies	hippuric acid	-0.45	<0.03
Neurocognitive Symptom			
Memory disturbance	alanine	-0.48	<0.02
Forgetfulness	aspartic acid	-0.46	<0.03
	proline	-0.44	<0.03
Trouble concentrating	β-amino-isobutyric acid	0.44	<0.03
Mind going blank	aspartic acid	-0.47	<0.02
	alanine	-0.41	<0.05
	aconitic acid	-0.41	<0.05
Mental confusion	β-amino-isobutyric acid	0.43	<0.04
	aspartic acid	-0.56	<0.004
	alanine	-0.51	<0.009
	valine	-0.43	<0.04
	hydroxyproline	-0.42	<0.04

Statistical method = Spearman Rank Order Correlation analysis. *n* = 25 and 37 for the IS and control groups respectively.

The perception of distortions in print are considered to be the primary feature of IS, which is thought to lead to the reading difficulties observed. Positive and negative associations between various excreted metabolites and reported print distortion and reading difficulty were revealed for the IS cohort. These results indicated that in some instances, as these problems became more severe, metabolite excretion increased. In other instances the opposite was true, with more severe symptom expression being accompanied by a reduction in the loss of a metabolite. Print distortion and reading difficulties, and an improvement in these problems with the use of coloured filters, were both positively associated with the contractile protein amino acid 3-methylhistidine. The associations with 3-methylhistidine indicated that symptom improvement was greater, and the symptoms more severe, when there was a relative increase in the excretion of this amino acid. The urinary excretion of the amino acid 3-methylhistidine is considered to be an indicator of protein catabolism (Nissen, 1997). The presence of both positive and negative correlations with a number of urinary metabolites indicates that the worsening of IS symptoms, and their improvement with the use of colour, was not simply associated with an overall loss of metabolites that could be explained, for example, by increased renal excretion. Instead, changes within the balance of amino acids and other urinary metabolites occurred in association with changes in symptom expression and this implies alterations in metabolic homeostasis in association with IS.

Significant associations between the relative abundance of urinary metabolites and the reported severity of the general health symptoms, that were more severe for the IS cohort, were also revealed. Both negative and positive correlations were again demonstrated, suggesting that the poorer general health of the IS cohort was associated with a change in metabolic homeostasis as revealed by alterations in metabolite excretion. The reported severity of photophobia was positively associated with the amino acid leucine whilst hippuric acid showed a negative association with the occurrence of allergies for the IS group. Difficulties with memory and concentration showed both positive and negative correlations with a number of amino acids. Negative associations with alanine and with the CNS excitatory amino acid aspartic acid were revealed for a number of the neurocognitive difficulties which were more prevalent for the IS group. A relative reduction in the excretion of these amino acids was therefore associated with a worsening of the neurocognitive problems experienced by the IS subjects.

Correlations between the relative abundances of the plasma lipids measured and the reported severity of the IS symptoms and the general health symptoms were determined for the IS cohort. Once again both positive and negative associations were revealed indicating a shift in the balance of the various lipids within the plasma of the IS group in association with changes in IS symptoms and with poorer health when compared to the control group. The *trans* fatty acid elaidic acid was associated with eyestrain and also with the severity of photophobia reported for a seven-day period. This result indicates that the higher the relative amounts of elaidic acid in the plasma of the IS subjects the greater the reported severity of eyestrain.

A number of significant associations were also revealed with those neurocognitive difficulties which were of greater severity for the IS group.

Table 4. Significant correlations between plasma lipids (percentage abundance) and core IS symptom severity, symptom improvement with IS lens use and with severity of general health questionnaire symptoms within the IS cohort

Reported Symptom	Plasma Lipid	Spearman R
IS Symptom		
Eyestrain	elaidic acid (*trans*, n-9)	0.40
	cis-11,14-C20:2 (n-6)	-0.44
	myristic acid (saturated)	-0.40
Eyestrain improvement	cis-11,14-C20:2 (n-6)	-0.45
General Health Symptom		
General Symptom		
Photophobia	elaidic acid (*trans*, n-9)	-0.51
Neurocognitive Symptom		
Memory disturbance	palmitoleic acid (n-7)	0.45
	myristoleic acid (n-7)	-0.42
	lignoceric acid (saturated)	-0.41
Trouble concentrating	myristoleic acid (n-7)	-0.42
Slowness to ensure correctness	lignoceric acid (saturated)	0.44
	cis-11,14-C20:2 (n-6)	0.40
	DGLA (n-6)	-0.62
	arachidonic acid (n-6)	-0.45
	oleic acid (n-9)	-0.41
Mental confusion	linoleic acid (n-6)	-0.49
	oleic acid (n-9)	-0.44
Double checking	lathosterol	0.47

Statistical method = Spearman Rank Order Correlation analysis. $p < 0.05$. $n = 25$ and 35 for the IS and control groups respectively.

The n-6 EFAs dihomogamma-linolenic acid (DGLA) and arachidonic acid (AA) were both negatively associated with "slowness to ensure correctness" indicating that the lower the relative amounts of these EFAs the more difficulty with neurocognition reported by the IS subjects. A positive association of the severity of the general health question "having to check and double check what you are doing" was revealed with the relative amounts of the cholesterol precursor lathosterol and may indicate an upregulation of cholesterol production.

In addition to the self-administered general health questionnaire all participants, or their parents in the case of the juvenile subjects, were interviewed and asked to answer a series of questions in regards to their medical histories including whether they had been born prematurely or to term. A significant increase in the occurrence of premature births was revealed for the IS cohort with 20% indicating (or their parents in the case of the juveniles) that they had been born prematurely in comparison to the control group in which no premature births were reported (Fisher Exact Probability $p < 0.009$).

The results indicated that the general "well-being" of the IS subjects was significantly poorer than that of their control counterparts. Biochemical analyses and correlation analyses revealed that the key features of the syndrome were associated with changes in the balance of urinary metabolites and were also associated with changes in the balance of plasma lipids, as were many of the general health questionnaire symptoms.

CONCLUSION

In comparison to the matched control group the IS subjects displayed an increased prevalence of problems with memory and concentration, mood, light sensitivity and symptoms suggestive of a possible increase in immune disorders or dysfunction. These findings in relation to dyslexia are not novel. However, the associations observed between these symptoms and plasma lipid composition and the excretion of urinary metabolites suggested that IS symptoms and poorer health were associated with alterations in metabolic homeostasis. Correlation analysis of course cannot be used to prove causation and it is only possible to speculate as to what the associations between symptoms and the urinary metabolites and plasma lipids may signify. In conjunction with the findings of previous IS, dyslexia and learning disability studies the findings of the present research may however give some insight into the underlying causes of this form of reading disability.

A number of the findings of the present study were in agreement with the known features of dyslexia, including the presence of cognitive weaknesses. The IS group reported an increased incidence of difficulties with memory and concentration and also with two symptoms suggestive of mood related problems. It could be argued that these symptoms may have arisen from the fact that the IS group were experiencing reading difficulties that were not present for the controls. However, the Cotton and Evans (1990) study revealed that IS children were more likely to exhibit anxiety and nervousness than a matched group of reading disabled children who did not have symptoms of IS. No associations between plasma lipid levels or urinary metabolites were revealed for the mood symptoms which were of greater severity for the IS cohort, although a number of significant associations were revealed with the severity of the neurocognitive difficulties reported by the IS subjects. Amongst the associations of the urinary metabolites and plasma lipids with neurocognitive problems were negative correlations with the amino acid aspartic acid and with the n-6 fatty acids DGLA and AA. The neuroexcitatory amino acid aspartic acid is found within the CNS and changes in its levels may have implications for neurotransmission. Arachidonic acid is involved in eicosanoid synthesis and inflammation. Arachidonic acid and docosahexaenoic acid (DHA) are the most prevalent of the brain's fatty acids and long chain polyunsaturated fatty acids are required for normal CNS development including cognitive and visual development (Makrides, Neumann, Simmer, Pater, and Gibson, 1995; see Willatts and Forsyth, 2000). In the present study an increase in "slowness to ensure correctness" was associated with a decrease in the plasma relative abundances of AA and DGLA. If the associated changes in plasma levels of the n-6 EFAs were reflected in the CNS lipid levels of the IS subjects, the lipid level changes may have contributed to the neurocognitive difficulties reported. No significant associations with n-3 fatty acids were revealed for the IS group in the present study, despite evidence that EFA deficiency is associated with symptoms of dyslexia (Richardson et al., 2000; Taylor et al., 2000) and that EFA supplementation can result in a range of improvements including in reading and spelling (Richardson and Montgomery, 2005; Stordy, 1995).

In the present study the IS group were shown to be "less well" than their control peers. The IS subjects recorded a significantly increased prevalence of recurrent mouth ulcers and allergies. Investigations of a possible association between learning disorders and immune and autoimmune disorders have produced conflicting results. Gilger et al. (1998) found no link

between developmental reading disorder and immune disorders and no evidence to suggest a common aetiology for the two. In contrast, other studies have supported an association between dyslexia and immune disorders such as allergic and atopic conditions (Hugdahl et al., 1990). In the present study a significant increase in symptoms associated with deficiencies in immune function were revealed for the IS group. Forty-four percent of the IS group reported being affected by allergies over the preceding week in comparison to only 10.8% of the control subjects. Although these results are hardly definitive, as data were collected by self-administered questionnaire, it is interesting to note that allergy severity reported by the IS cohort showed only one significant association, which was with the detoxification compound hippuric acid. Hippuric acid, or benzoyl glycine, is produced in the liver by conjugation of glycine with the potentially toxic compound benzoic acid, which is then excreted in the urine (Bender, 1985). Benzoic acid, which is present in many foods as a preservative, can cause allergic reactions. The negative correlation between reported allergy severity and the relative abundance of hippuric acid suggests that as allergic symptoms increased there was an accompanying reduction in the excretion of hippuric acid for the IS subjects. It could be proposed that a reduction in the excretion of hippuric acid may reflect an impaired ability to excrete toxic metabolites via conjugation reactions, with an accompanying increase in allergic symptoms.

Sensitivity to light has been commonly reported by people with IS, with fluorescent lighting and high contrast print claimed to exacerbate the visual-perceptual problems experienced whilst reading (Irlen, 1991). In the present study, leucine was the only urinary metabolite found to be associated with the severity of photophobia reported over a seven-day period. In a previous study in which urinary metabolite levels were determined for a group of CFS patients identified from a questionnaire as likely to have symptoms of IS, leucine was also the only metabolite found to be associated with photophobia (Robinson, Roberts, McGregor, Dunstan, and Butt, 1999). Leucine is an essential amino acid and can act as a regulator of protein metabolism (McGregor, De Becker, and De Meirleir, 2002). The catabolism of skeletal muscle proteins can occur in response to events such as trauma and infection, resulting in the release of their constituent amino acids into the circulation. The amino acids 1-methylhistidine and 3-methylhistidine are constituents of skeletal muscle contractile proteins. In particular 3-methylhistidine is unique to the cytoskeleton proteins actin and myosin and is therefore considered to be a reliable indicator of muscle fibrillar protein catabolism. Increased release of this amino acid into the circulation, followed by an accompanying increase in its excretion into the urine, can occur in response to the release of cytokines, the interleukins IL-1 and IL-6 (Graham, 2001).

In the current investigation the severity of print distortion and reading difficulty, and the improvement in these symptoms with the use of coloured lenses, were positively associated with 1-methylhistidine and/or 3-methylhistidine. The results indicate that as the excretion of a marker of protein catabolism increased, so did the severity of two of the key symptoms of IS and that a more marked improvement in these difficulties was also seen with the use of coloured filters. Differences in the excretion of 3-methylhistidine were also found in a group of CFS patients who had been diagnosed with IS (Robinson et al., 2001). The CFS/IS subjects were also found to have an increase in sore and swollen lymph nodes indicative of the presence of an infection. The authors speculated a link could be drawn between protein catabolism, as indicated by the presence of markers of proteolysis, and an activation of the immune system and accompanying cytokine production in IS. They suggest that these events,

triggered by infection, may have had implications for the visual dysfunction seen in IS (Robinson et al., 2001). In the present study the associations between reading difficulty and reported severity of print distortion with 3-methylhistidine support an association between an immune response to infection and IS symptom expression. The possibility of an immune system dysfunction in association with IS was also supported by the increased prevalence of mouth ulcers, an indicator of viral reactivation (McGregor et al., 2002), and the accompanying increase in other symptoms commonly seen during infection such as sore and swollen lymph nodes.

A significant increase in the prevalence of recurrent mouth ulcers was recorded for the IS cohort and the severity of recent mouth ulceration was also positively correlated with other symptoms indicative of infection. Although these results and the association between IS key symptoms and indicators of protein catabolism may be interpreted as the presence of chronic infection in IS, infection may not be the underlying cause of the changes in visual processing experienced in IS. Deficiencies in EFAs, in particular DHA and eicosapentaenoic acid (EPA), have been suggested as a causal mechanism of dyslexia and related conditions such as ADHD. However, in the present study no associations between the n-3 fatty acids DHA or EPA and the key IS symptoms or any of the other general health problems were shown for the IS cohort that were different from those of the control group. Essential fatty acids are necessary for the functioning of the immune system and it has been suggested that EFA treatment may work to reduce inflammation in neurodevelopmental disorders such as dyslexia (Taylor, 2002).

The fatty acid elaidic acid (*trans*-9-C18:1) was associated with the severity of eyestrain assessed during the IS diagnostic process and with photophobia reported by the IS subjects for a seven-day period. The positive association between the reported degrees of eyestrain was supported by previous research. Robinson et al. (2001) found that the relative abundance of elaidic acid was increased for a group of CFS patients with IS who had high symptoms and positive responses to coloured filters in comparison to a low symptom group who responded negatively to the use of colour. Elaidic acid is a *trans* fatty acid and although it occurs naturally it is found in the modern diet occurring mainly in processed foods containing hydrogenated oils. Elaidic acid accounts for the majority of *trans* fatty acids found in the modern diet. *Trans* fatty acids are known to be associated with a number of health problems including heart disease and diabetes. Although their role in pathogenesis is still under investigation, their inclusion into cell membranes can alter cell membrane fluidity and function; they are known to have an inhibitory effect on EFA metabolism and can alter eicosanoid biosynthesis. Higher dietary intake and higher relative levels of elaidic acid in erythrocyte membranes of women have been associated with an increased risk of preeclampsia during pregnancy (Williams et al., 1998). In one study of healthy women high dietary *trans* fatty acid intake was found to be positively associated with higher concentrations of markers of inflammation independent of serum lipid concentrations and other factors known to affect systemic inflammation (Mozaffarian et al., 2004). Mozaffarian et al. (2004) concluded that the dietary intake of *trans* fatty acids was positively associated with systemic inflammation.

In the present study, the positive association between elaidic acid and eyestrain, and the increase in elaidic acid in the plasma of a high IS symptom group of CFS patients identified by Robinson et al. (2001) indicated that higher levels of this *trans* fatty acid were associated with an increase in IS symptom severity. In contrast, a negative association with elaidic acid

was seen in the present study with the reported severity of photophobia experienced by the IS cohort over the week leading up to the collection of the blood sample. This result suggests that an increase in perceived light sensitivity was accompanied by reductions in plasma levels of elaidic acid. Investigations of plasma lipid levels in CFS patients has revealed a significant reduction in elaidic acid compared to controls (Dunstan et al., 1999) and that a reduction in this *trans* fatty acid was the primary discriminating factor for the control and CFS subjects (McGregor et al., 2000). It has been suggested that symptom expression in CFS may result from virus reactivation, with CFS patients often reporting a sudden onset of the syndrome following a viral-like illness (McGregor et al., 2000). As it has been reported that elaidic acid may be virucidal (Horowitz et al., 1988) Dunstan et al. (1999) suggested that viral infection could result in a depletion of elaidic acid, which in turn could result in an increased vulnerability to viral infection or reactivation in the future.

It has been suggested that children born prematurely are at an increased risk of developing dyslexia. Bowen, Gibson and Hand (2002) found that for a group of 8 year olds, with normal or above average intelligence who had been born extremely prematurely, their academic abilities including reading and spelling were significantly poorer than their peers who had been born to term. It was interesting to note that in the present study, the dyslexic cohort reported a significantly higher rate of premature births in comparison to the control group. Individuals diagnosed with dyslexia are thought to represent a heterogeneous group. Those individuals presenting with IS after the onset of CFS and others reporting premature birth may form subgroups within the IS subtype itself. Research regarding the aetiology of learning disabilities, such as dyslexia, may be hampered by a lack of homogeneity within the study groups. Further research to allow for the identification of possible subtypes may therefore be justified.

The various associations revealed between the urinary metabolites and the plasma lipids measured and the symptoms experienced by the IS cohort are open to interpretation. The results of the present study however indicate that individuals with a diagnosis of IS are more likely to experience problems ranging from recurrent viral infection to problems with memory and concentration and that many of these difficulties were associated with changes occurring at a biochemical level. No conclusions can be drawn regarding the individual associations identified between symptoms and the excreted metabolites and plasma lipids, however the results support the presence of alterations in metabolic homeostasis in IS. The validity of IS as a legitimate diagnostic category and the efficacy of coloured lenses in improving reading difficulties in some individuals have attracted much criticism. Changes in metabolic homeostasis associated with the key identifying features of IS and other difficulties of increased prevalence suggest that further work is warranted in this area. A high degree of clinical heterogeneity is known to exist in dyslexia and the identification of subtypes will aid in the search for solutions to reading disability. Identifying possible changes in metabolic processes in IS will not only contribute to an understanding of the aetiology of reading disability but may also allow for the wider acceptance of this visual-perceptual subtype of dyslexia.

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Chapter 5

LEARNING DIFFICULTIES AND BRAIN TUMORS

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ABSTRACT

Brain tumours affect approximately 1 in 2,000 children. In recent years, survival rates have improved for these children, leading to an increased focus on longer term social and educational prospects. The combined effects of the initial tumour, and aggressive treatments (radiotherapy, surgery and chemotherapy) necessarily mean that many survivors will experience long-term learning difficulties including IQ, memory and attention problems. Social, emotional and behavioural issues may also compromise academic achievement. Whilst the special needs of this population have been recognised for a long time, there has been no national programme developed to rehabilitate survivors or provide educational support. Teachers maybe uncertain how to respond to a child who has had a brain tumour and lack the knowledge or understanding necessary to provide appropriate education. Furthermore, standard educational support methods maybe poorly tuned to the needs of brain tumour survivors. It is therefore imperative that the learning difficulties of these children are described in detail and recommendations made for their remediation. This chapter details the skills and deficits of a group of 40 brain tumour survivors. Areas of functioning assessed included reading, IQ, memory, attention and learning. Information on school attendance, peer relationships and mother and teacher perceptions of behavioural, social, physical and educational needs is also presented. The findings point to specific cognitive issues for brain tumour survivors, including compromised verbal skills, IQ, memory and literacy. Information processing skills including attention/concentration, learning and speed of processing are also affected. Results also highlight a shortfall between deficits and remediation. The high prevalence of behavioural, social and emotional problems is also discussed. Compromised learning ability means that survivors will require special help to acquire new skills and information. Recommendations for such help, including the use of visual aids to support learning and more time to complete tasks both in class and in tests are made.

INTRODUCTION

A significant number of children who have special educational needs (SEN) in schools, have learning difficulties (LD) as a consequence of medical problems such as low birth weight, cerebral palsy, autism, epilepsy and childhood cancer. The problem of LD after cancer has been associated with certain treatment regimes, especially the use of cranial radiation therapy (CRT) [Butler, Hill, Steinherz, Meyers and Finlay, 1994], although other factors such as gender and age at which CRT is administered are thought to influence the extent to which cognitive functioning will be affected. Recent evidence suggests that girls and younger patients are more vulnerable to deficits [Leung et al., 2000; Ris, Packer, Goldwein, Jones-Wallace, and Boyett, 2001]. These findings have led to changes in treatment protocols – for example CRT is no longer routinely given to children under 3 years of age and alternative treatments are used where possible [Butler and Mulhern, 2005]. However, there is now evidence to suggest that whilst chemotherapy is less harmful to the child's neurological and cognitive status than CRT, certain chemotherapy agents such as the corticosteroid dexamethasone are neuro-toxic and have been implicated in increased cognitive late effects [Waber et al., 2000]. Thus, despite attempts to reduce morbidity whilst maintaining remission rates, the incidence of LD after cancer remains unacceptably high [Mulhern and Palmer 2003].

Treatment regimes are, however, not the only cause of LD after cancer. Other risk factors for LD include the nature of the cancer; cancers with actual or potential central nervous system (CNS) involvement such as acute lymphoblastic leukemia (ALL) and brain tumours put children at far greater risk of LD than for example, soft tissue or bone tumours. It should not therefore be assumed that a diagnosis of cancer automatically leads to difficulties in the classroom. However it must be acknowledged that for certain groups there is considerable evidence that LD are a risk. According to Butler and Mulhern [2005], whilst the combined effects of cancer and cancer therapy may lead to LD in children who have had either ALL or brain tumour, children who survive brain tumours are at greater risk for more severe deficits compared to survivors of ALL, because of the more aggressive nature of their therapy including the invasiveness of surgery and the continued use of CRT. Thus whilst the incidence of LD after chemotherapy treatment for ALL has been estimated by some to be around 30% [Copeland, Moore, Francis, Jaffe, and Culbert, 1996], for brain tumour survivors LD are estimated to be around 50% [National Cancer Institute, 2001]. Survivors of brain tumours, for example, show poorer IQ, greater problems with learning and memory and more behaviour problems than healthy children [Mulhern et al., 1989; Lannering, Marky, Lundberg and Olsson, 1990; Steinlin et al., 2003]. They are also at increased risk of a poorer quality of life (QOL) than their healthy peers [Mostow, Byrne, Connelly and Mulvihill, 1991] as well as children who have survived other forms of cancer [Eiser, Vance, Horne, Glaser and Galvin, 2003]; it maybe that difficulties experienced at school play a part in this compromised well-being. It is important therefore, that remedial programmes are developed which are appropriate for the nature and degree of difficulty experienced by these children. Indeed, recent reports and NHS guidance, emphasizes the need for continued psychological care of survivors of childhood cancer, including recognition, assessment and remediation of learning and psychosocial problems [*www.sign.ac.uk*].

In this chapter we outline the incidence, diagnosis and treatment of childhood brain tumours before summarising previous literature on LD in these children. We then describe a recent study of 40 survivors of childhood brain tumour, documenting family experiences of return to school, as well as the children's cognitive and psychosocial functioning.

INCIDENCE AND CLASSIFICATION OF TUMOURS

Brain tumours are the most common solid tumours of childhood, affecting approximately 1 in 2,000 children. Although survival rates for children with brain tumours have improved in recent years, they still are significantly below survival rates for other childhood cancers. Brain tumors can develop at any age, but are most commonly seen in children between the ages of 3-12 years. Prevalence is also somewhat greater for boys than girls.

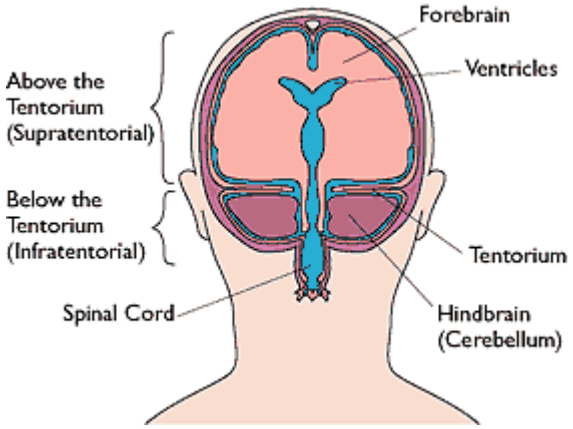

Figure 1. (from *http://www.cancerhelp.org.uk*)

Brain tumours are often described by their location: supratentorial tumours are located in the upper part of the brain and account for 40% of childhood brain tumours. Infratentorial or posterior fossa tumours are found in the lower part of the brain and account for the majority of childhood brain tumours (60%). However, classification of brain tumours is more usefully based on a number of complex criteria, including clinical course and histopathology [Collins, 2004]. According to the most recent classification system introduced by the World Health Organisation in 2000, the most common childhood tumours are astrocytoma, ependymoma and medulloblastoma. Childhood astrocytomas most commonly occur in the cerebellum (an area in the lower part of the brain) and are generally biologically non-aggressive (benign). Astrocytomas that can be surgically excised therefore tend to have a good prognosis. Ependymomas may occur anywhere in the ventricular system and the spinal canal, although the most common location is in the fourth ventricle, which is located in the posterior fossa. There are a number of subtypes, ranging from the benign tumours most frequently seen in childhood, to rapidly growing malignant tumours. Medulloblastoma is the most common brain tumour of childhood. These are highly malignant invasive tumours, occurring almost exclusively in the cerebellum.

DIAGNOSIS AND TREATMENT

Brain tumours are notoriously difficult to diagnose. Symptoms resemble those of many other illnesses and often include recurrent bouts of headache, nausea and vomiting. These symptoms suggest the presence of increased intracranial pressure and are particularly common with posterior fossa tumours. The headaches increase in frequency, are more severe in the morning, and are typically followed by vomiting. Symptoms can be debilitating and may cause frequent absences from school. Specific neurological symptoms, such as ataxia, hemiparesis, or progressive deterioration of sight, speech, hearing etc may occur later in the illness and can also interfere with daily activity. The non-specificity of early symptoms means that there is a high risk that parents will delay seeking medical advice and that physicians will not instigate diagnostic investigations for brain tumour on a child's first presentation. Unexplained vomiting, for example, may be mistaken for a gastrointestinal problem. Misdiagnosis of migraine is also common to approximately a quarter of cases [Edgeworth, Bullock, Bailey, Gallagher and Crouchman, 1996]. Research has indicated that the mean time from onset of clinical history to diagnosis may be up to 20 weeks, with the involvement of different specialties before a final diagnosis is made [Saha, Love, Eden, Micallef-Eynaud and MacInlay, 1993]. Diagnosis is especially difficult in small children, who may have difficulty explaining their problems. In school-aged children, symptoms can be confused with reluctance to go to school and a diagnosis of psychosomatic illness is not uncommon [Edgeworth et al., 1996].

Following diagnosis, the goal is to remove as much tumour as is safely possible through surgery. In the case of malignant tumours this may be followed by a period of chemotherapy and/or CRT with the goal to eradicate any remaining tumour and limit further growth. CRT is typically delivered once a day, 5 days a week, for up to 6 weeks [Butler and Mulhern, 2005]. Radiation may be given either specifically to the site of the tumour itself or to the whole brain and spinal cord with a boost given at the tumour site. CRT for primary brain tumours tends to be given in higher doses than for other malignancies or for ALL [Anderson, Godber, Smibert, Weiskop, and Ekert, 2000]. Chemotherapy treatment regimes vary but are usually given in cycles so that there is a recovery period following each treatment phase. A total course usually lasts several months [see Pollack, Boyett and Finlay, 1999 for a comprehensive review of typical protocols]. As noted above, CRT is avoided for children under the age of 3 years, with maintenance chemotherapy being the preferred treatment method, until the child is old enough for CRT. Treatment can therefore include any combination of chemotherapy, radiotherapy and surgery and is dependent on the age of the child, as well as the site and grade of the tumour.

LEARNING DIFFICULTIES AFTER CANCER

Contemporary research distinguishes two types of cognitive functioning problem; core deficits and secondary deficits [Butler and Mulhern, 2005]. Core deficits include executive functions and information processing abilities such as memory and attention. It is suggested that deficits in core areas are a result of observable brain damage caused by the disease and its treatment; several studies have demonstrated an association between a reduction in the

volume of white matter of children with brain tumours and loss of core cognitive functions [e.g. Reddick et al., 2003]. Secondary deficits are knowledge based and include easily measurable difficulties in areas such as reading, maths and IQ. These are suggested to be symptomatic of the loss of core functions, rather than being directly caused by disease or treatment [Schatz, Kramer, Ablin and Matthay, 2000; Reddick et al., 2003].

The most frequently reported core cognitive deficits involve attention or concentration deficits [Steinlin et al 2003, Reddick et al 2003**].**Other deficits that have been noted include memory and information processing speed [Schatz et al., 2000] although investigations into memory problems has been limited until relatively recently, due to the lack of a comprehensive, standardized measure of memory for children [George et al., 2003]. Such impairments have been suggested to result from the brain damage caused by treatments such as CRT and chemotherapy [eg Mulhern et al., 1999]. However it is clear that these therapies alone cannot explain loss of core cognitive functioning. Deficits in executive functioning and memory, have for example, been noted in brain tumour survivors who have not been treated with either chemotherapy or CRT [Levisohn, Cronin-Golomb and Schmahmann, 2000]. As Reddick et al. [2003] note, reduced white matter volume may represent the impact of various sources of brain damage, which include increased intracranial pressure resulting from tumour growth as well as treatment approaches such as steroids, CRT and chemotherapy.

Evidence of secondary deficits such as below average IQ following treatment are common throughout the literature [e.g. Riva, Pantaleoni, Milani and Belani, 1989; Lannering et al., 1990]. Poor academic achievement has also been demonstrated with problems in reading, writing and arithmetic being indicated [Johnson et al., 1994; Kimmings, Kleinlugtebeld, Casey and Hayward, 1995]. The high rate of specific LD and the associated need for help in school for these children has also been noted [e.g. Packer et al., 1989; Radcliffe, Bennett, Kazak, Foley and Phillips, 1996]. However the demonstration of links between core deficits and secondary deficits is relatively recent. Difficulties with maths shown after treatment for ALL for example, have been related to problems with memory and psychomotor processing speed [Kaemingk, Carey, Moore, Herzer and Hutter, 2004], whilst lowered IQ levels have been linked to a deficit in attention/concentration [Reddick et al., 2003]. Further evidence from studies of children without brain damage has demonstrated the role of memory skills in reading and comprehension [Caplan and Waters, 1999]. Furthermore, it is widely accepted that certain aspects of IQ measurement are based on prior knowledge and therefore memory function. Such evidence makes the theory that problems with IQ and academic performance are secondary to attention and memory deficits seem persuasive. However, it should be noted that whilst remediation has been shown to improve attention and concentration in this population, generalisation of this improvement to academic achievement has not been demonstrated [Butler and Copeland, 2002], suggesting that the link between core and secondary deficits is not a simple one. Thus from a practical stance, it seems important that remediation for both core and secondary deficits is provided for these children.

It has been suggested that the cognitive deficits shown by brain tumour survivors may impact other areas of functioning, such as social interactions [Vannatta, Gartstein, Short, and Noll, 1998]. There is some support for the idea that cognitive deficits are at the root of social problems; it has been hypothesized that cognitive impairments hinder the understanding of social cues and relationships [Nassau and Drotar, 1997]. However, it should be noted that this is a purely theoretical stance and so whilst co-morbidity of social problems and LD has been shown [e.g. Abrams, 1986] a direction of effect is not proven.

RETURN TO SCHOOL

School attendance is assumed to be important in facilitating a more normal life for child and family. It is a context in which children can be themselves less inhibited by constraints of illness, and where they have the opportunity to be with peers. School attendance is also important in the long-term, to the extent that opportunities for future employment and long-term integration in adult life are dependent on school achievement.

Return to school after diagnosis can be difficult. Many brain tumour survivors have special needs and it has been estimated that approximately 50% will need help in the classroom [National Cancer Institute, 2001]. This may be because of learning difficulties or because physical problems limit their ability to move round the school. Changes in physical appearance are an inevitable consequence of treatment, and may be associated with teasing. The child may be unable to take part in the whole curriculum. They may simply be physically unable to take part in PE or other sports activities or feel tired and miss out on activities. Children are typically seen to be isolated, sensitive and lacking in energy [Noll, Ris, Davies, Bukowski and Koontz, 1992; Vannatta et al., 1998] and many of these initial difficulties remain problems for long-term survivors too.

Added to this, teachers are often uncertain how to respond to the child and anxious about how other children will react to the presence of a child with a life-threatening condition. At the end of treatment, children are often expected to be ‘back to normal’ and achieve as much as other children. In reality, they may remain at considerable disadvantage both physically and educationally because of the combined effect of the initial tumour, radiotherapy and chemotherapy as described earlier.

It has been shown that children with chronic health problems, even those that do not have CNS involvement, perform less well academically than their healthier peers and the evidence suggests that absence from school is one factor behind this discrepancy [Fowler, Johnson and Atkinson, 1985]. School absence is a problem for children with cancer in all stages of their illness both during [Charlton et al., 1991] and after completion of treatment [Noll et al., 1990] and it is not unusual for them to miss as much as 3-12 months of school after diagnosis. Debilitating symptoms may also cause many children to have frequent absences from school before diagnosis. Reasons for missed schooling after diagnosis include infections, hospital appointments and the effects of treatment such as feeling unwell or tired. Children may also stay away if there is an increased risk of infection, for example when a child in their class is unwell. When treatment is over there may be difficulties returning to school [Katz, Varni, Rubenstein, Blew, and Hubert, 1992; Tuffrey, Muir, Coad, and Walker, 1993] and many children will initially return to school on a part-time basis; getting back to school full time may take many months. Long absences from school mean that children will fall behind their classmates and performance is most likely to be affected in subjects such as literacy and numeracy that build on previous knowledge and skills [Chekryn, Deegan, and Reid,1986].

Thus, for children who have had a brain tumour, the school experience may fall short of the ideal. Given the contribution of school experiences to educational achievement and social adjustment, it is clearly important to document both the nature and extent of the difficulties experienced by these children. Whilst retrospective studies [e.g. National Cancer Institute, 2001] provide some indication of the extent of problems, they are no substitute for studies with current survivors. Unfortunately, research considering the school functioning of children

diagnosed with cancer often excludes children with brain tumours [e.g. Noll et al 1999, Bessell, 2001]. In order to redress this balance and further motivated by the remarks made by parents of survivors concerning the range of educational and social problems experienced by their children at school, we undertook a study to describe the school functioning of a group of brain tumour survivors. In this chapter we:

- describe the special educational needs (SEN) of these children and their families' experiences of the special needs system[1],
- describe frequently documented cognitive deficits including memory and concentration, literacy and IQ,
- compare current SEN provision and cognitive functioning needs identified through memory and concentration, literacy and IQ testing,
- document the impact of diagnosis and treatment on school attendance and experiences on return to school,
- assess mother and teacher evaluations of children's social emotional and behavioural difficulties.

METHODS

Design

The cognitive and psychosocial functioning of a cross-sectional sample of 6-16 year old CNS tumour survivors were assessed using psychometric and survey methodology.

Measures

Cognitive functioning was assessed with a comprehensive battery of psychometric tests which included the following:

Children's Memory Scale (CMS) [Cohen, 1997]. Suitable for children aged 5-16 years. Includes sub-tests to assess immediate and delayed visual and verbal memory, delayed recognition, attention/concentration and learning.

Wechsler Objective Reading dimensions (WORD) [Rust, Golombrok and Trickey, 1993]. Suitable for children aged 6-16 years. Standardised scores were calculated for reading and comprehension skills.

[1]In the UK, there is a five stage approach to identifying and supporting children with SEN. Initially it is the school's responsibility to identify children who may have SEN (Stage 1). If an initial support plan does not lead to significant progress, the school's SEN Coordinator (SENCO) should construct an Individual Education Plan (IEP) for the child (Stage 2, sometimes referred to as 'School Action'). The IEP typically prescribes a structured, targeted, support programme, including provision of external help if necessary. If it is found that a child is not making adequate progress, or if a child's special educational needs cannot be met under School Action, then specialists may be consulted and new teaching strategies developed.(Stage 3, sometimes referred to as 'School Action Plus'). If this still fails to lead to significant progress after at least six months, the child should be referred for a Statutory Assessment of SEN (Stage 4). The Assessment may then lead to a '*Statement of SEN'* for the child (Stage 5). This in turn leads to the development of an ongoing support and monitoring programme. The process of obtaining SEN support is therefore sometimes referred to as *'Statementing'*

Wechsler Intelligence Scale for Children, version III (WISC) [Wechsler, 1992]. Suitable for children aged 6-16 years. Includes assessment of *Verbal* tasks, based on what a child has learnt, and their ability to use and express this knowledge; and *Performance* tasks, which reflect abilities in a number of areas including non-verbal reasoning, handling novel information, fine motor skills, sequencing and speed of working. Standardised scores were calculated for Verbal, Performance and Full-scale IQ.

The above tests are all standardised with a population mean of 100, and standard deviation of 15. Thus, an average score is within the range of 85 to 115. Scores of 2 standard deviations or more below the mean (i.e. 70 or less) are said to be exceptionally low.

Educational needs, school attendance, experiences and psychosocial functioning after diagnosis and treatment were assessed through interviews with mothers, and questionnaires completed by both mothers and teachers as follows:

- **Mother's Semi-Structured Interview**

  Interviews were organized round three time periods: before diagnosis, immediately after diagnosis and the current time. Questions focused on school attendance, peer relationships and perceptions of physical and educational needs.

- **Teacher Questionnaire**

  Teachers completed a brief questionnaire concerning present and past SEN and clarifying the child's current status (e.g. has a formal statement of needs been given or were needs being met through school action?).

- **Strengths and Difficulties Questionnaire (SDQ) [Goodman, 1997].**

  Both mothers and teachers completed the SDQ. This is a brief screening questionnaire for children aged 3-16 years. The SDQ is both valid and reliable and has been shown to discriminate between children with mental health problems and community controls [Goodman 1997; Goodman et al 1998; Meltzer, Gatward, Goodman and Ford 2000]. The SDQ asks about 25 attributes, some positive and others negative. These 25 items are divided equally between 5 scales: emotional symptoms (items include frequency of worrying, unhappiness and fears), conduct problems (items include frequency of temper tantrums and bullying), hyperactivity/inattention (items include distractibility and attention span), peer relationship problems (items include friendships, social isolation and being bullied) and pro-social behaviour (items include sharing, helping and consideration of others feelings). A total difficulties score is calculated by summing the scores from all the scales except the pro-social scale. High scores indicate a problem on all scales except pro-social behaviour, where difficulties are indicated by lower scores. UK population norms are available [Meltzer et al., 2000].

PROCEDURE

Ethical Approval was Obtained from the Local Research Ethics Committees in Sheffield and Cardiff.

Letters were sent to families of all eligible children inviting them to take part in a research project to determine the difficulties experienced by children on return to school after a brain tumour. Families who responded positively to this initial letter were given written and verbal information either in clinic or during a home visit. Following written consent mothers took part in a semi-structured interview and completed SDQ, and children completed an extensive battery of cognitive and memory tests as described above. The tests and questionnaires were administered over two sessions, each lasting approximately an hour. Assessments took place at the child's home, at times convenient to the family. Families were also asked for permission to contact the child's school and invite their teachers to take part in a postal survey.

Treatment Of Results

Mean scores for WORD, WISC and CMS were calculated according to standard manuals and compared with population norms [Rust et al., 1993; Wechsler, 1992; Cohen, 1997]. Descriptive statistics were calculated for SEN, and school attendance both during the diagnosis and treatment period and the past school year. SDQ was calculated according to standard instructions and mother and teacher scores were compared to published UK population norms [Meltzer et al., 2000].

RESULTS

Sample

Sixty-eight children who had completed therapy for a brain tumour at least 2 years previously in either Sheffield or Cardiff were identified through medical records. A total of 40 families agreed to participate (response rate=58.8%). The survivors included 19 males and 21 females aged from 6-16 years (mean age=12 years 2months, sd=30.15). Age of diagnosis ranged from 3 months to 13 years of age (mean age of diagnosis=6 years 4months, sd=36.81). Time since treatment ended ranged from 2 years to 12 years 5months (mean length of time since treatment ended=5 years 7months, sd=32.95). The most common diagnosis was for medulloblastoma (45%) and astrocytoma (17.5%). Ependymoma had been diagnosed in 5% of our sample. The remaining 32.5% of children had been diagnosed with other less common childhood tumours. Mother's reports indicated that 29 of the children (72.5%) had on-going neurological impairments resulting from the tumour and its treatment. The most common problems were related to movement and included ataxia (13 children), hemi paresis (6) and hemiplegia (4). Sensory problems were also common and included vision (9) and hearing (3). Speech was a problem for 2 children. Five suffered from epilepsy. Multiple difficulties were seen in 9 children.

EDUCATIONAL NEEDS

Thirty-three children attended mainstream schools, two were at private school and five attended special schools. Families provided information about all 40 schools and 29 of the schools returned completed questionnaires (response rate=72.5%). The majority of questionnaires were completed either by the child's class teacher (N=11) or the school's Special Education Needs Coordinator (SENCO) (N=10). One form was completed by the head of year, two by head teachers and four by support assistants. One respondent did not provide this information. Only one child had been identified as having SEN (dyslexia) before diagnosis, compared with 31 children (77.5%) after diagnosis. An Individual Education Plan (IEP) had been drawn up for 28 of the 31 children with SEN and 26 had a formal statement of needs. A considerable number of children needed help with physical difficulties such as getting around school and involvement in sports (17), visual problems (3) and speech (5). Specific LD included literacy (17), numeracy (9) and memory and concentration (5). Social and behavioral targets had been set for 8 children and included social skills (4), confidence (3) and reducing aggression (1). Three children had increasing school attendance as a target. Twenty-two children had multiple targets.

Nineteen mothers described difficulties getting SEN support. For example, when asked about provision of support at school one mother stated:

> 'He has to have CSA support. I had to fight for him to go through the statementing process to achieve that.'

Similar problems were described by other mothers. The main difficulty seemed to concern local authority systems and a lack of understanding of the special needs of brain tumour survivors:

> 'I was assured that he would be given help, but he wasn't, I don't think anybody understands children with needs such as these.'

In general, schools themselves were seen as supportive, although 8 mothers described difficulties having their child accepted back at school and 4 had moved their child to a different school because of this. The remaining mothers all felt schools had been supportive, even if they had been unsure of how to cope at first. Three mothers felt schools still over reacted on occasions, sending their child home at the least complaint of illness.

COGNITIVE FUNCTIONING

Sample means for all cognitive tasks are given in table 1. Sample means fell below the average band for all measures except reading and 3 subscales of the CMS (immediate and delayed visual memory and learning), although these scores were all at the lower end of the normal range. T-tests demonstrated the significance of differences in reading and comprehension ($t=4.05;df=38,p<0.001$) and spelling and comprehension ($t=3.45;df=38, p<0.01$). Verbal IQ was significantly better than performance IQ ($t=3.14;df=39,p<0.01$) and

immediate visual memory was significantly better than verbal memory ($t=2.20;df=34$, $p<0.05$).

Table 1. Sample means and comparison with norms for CMS, WORD and WISC

Area of assessment	Total Sample mean (sd)	% scoring below average (<85)	% scoring in the average band (85-115)	% scoring above average (>115)	% unable to be assessed
CMS					
General Memory	81.6(21.3)*	55.0	25.0	7.5	12.5
Concentration/ attention	82.5(20.4)*	40.0	45.0	2.5	12.5
Learning	85.9(16.8)*	40.0	45.0	2.5	12.5
Immediate visual memory	88.3(16.9)*	35.0	47.5	5.0	12.5
Delayed visual memory	89.3(16.1)*	40.0	42.5	5.0	12.5
Immediate verbal memory	82.2(19.4)*	52.5	32.5	2.5	12.5
Delayed verbal memory	83.1(21.6)*	48.0	32.5	7.5	12.5
WORD					
Reading	85.3(20.0)*	45.0	45.0	7.5	2.5
Spelling	84.3(18.7)*	50.0	42.5	5.0	2.5
Comprehension	69.5(35.9)*	32.5	45.0	2.5	20.0
WISC					
Verbal IQ	80.4(18.7)*	62.5	35.0	2.5	0.0
Performance IQ	73.2(18.7)*	72.5	25.0	2.5	0.0
Full Scale IQ	74.6(18.8)*	77.5	30.0	2.5	0.0

*Sample mean significantly different from standardized mean of 100 at $p<0.001$

Results from the cognitive assessment also highlighted literacy skills as a problem, with many of the sample demonstrating problems with reading, spelling and comprehension; for example, over half of the sample was experiencing difficulties with comprehension - 32.5% of the sample scored below average, whilst a further 20.0% were unable to be assessed due to their poor reading skills. IQ and memory skills were also found to be weak in our sample; over half of the children obtained below average IQ scores, whilst over half the sample either scored below the average range for general memory or did not have the capacity to complete the memory assessment. Memory problems also seemed to be impacting on daily life as 21 mothers mentioned poor memory as a problem for their child.

COGNITIVE FUNCTIONING AND EDUCATIONAL NEEDS

The group of children with literacy identified as an educational need had a significantly lower mean score for reading spelling and comprehension than those not targeted for literacy (see table 2). However consideration of individual scores showed that whilst 16 out of the 17 children with literacy targets scored below average on at least one of the WORD subtests (1 child achieved low average scores), not all children who scored below average had a literacy target (N=4). The children with memory and concentration as a target scored less on CMS general memory and concentration/attention subscales than those not targeted for memory and concentration, although these differences did not reach significance (see table 3). Furthermore, both groups scored below average on general memory. Consideration of individual scores showed that all the children with concentration and memory specified as an educational need scored below average on at least one of the relevant CMS subscales, however over half of the children who were not targeted for memory or concentration problems also scored below average on at least one of these subscales.

Table 2. Comparison of WORD mean scores for children with and without literacy targeted on their IEPs

	Literacy target	Mean score (sd)	Mean Difference	t
Reading	No	99.1(17.2)		
	Yes	72.7(13.3)	26.4	4.6*
Spelling	No	96.2(18.7)		
	Yes	74.5(12.3)	21.8	3.7*
Comprehension	No	92.2(15.9)		
	Yes	54.4(35.6)	37.8	3.7*

* significant at 0.001

Table 3. Comparison of CMS mean scores for children with and without memory targeted on their IEP

	Memory/concentration target	Mean score (sd)	Mean Difference	t
General memory	No	83.4(20.7)		
	Yes	74.3(24.8)	9.2	0.79
Concentration/ attention	No	87.7(20.2)		
	Yes	81.8(13.4)	6.0	0.57

IMPACT OF ILLNESS AND TREATMENT ON SCHOOL ATTENDANCE

Only those children diagnosed before school age had not missed any schooling because of illness or treatment (N=12). For the remaining 28 children diagnosis had taken anything from 6 weeks to 4 ½ years, during which time symptoms such as headache and sickness had led to regular school absences. Following diagnosis, further absence from school was incurred because of treatment, which ranged in length from 2 months to 2 years. Following treatment, most children either returned to school on a part time basis, or had a home tutor. The length of time spent in part time education varied from a month to 2 years, depending on the provision made by local education authorities. Two children, both of whom were 2 years post-treatment, were still attending school on a part time basis at the time of the study, whilst one girl who had completed treatment 6 years earlier had stopped attending school because she felt she could no longer cope with the work. None of the children who returned to mainstream school had repeated a school year.

Difficulties for the child on return to school were described by 11 mothers. Most difficulties described were social:

> 'And at the beginning for him, I mean he never had a hair on his head, he was in a strange class, and I'd go and sit outside [the school] at lunch-time and he'd be on his own and I'd cry and … because nobody wanted to play with him because he didn't have no hair.'

and

> 'So he has been isolated because of his illness and just lacks confidence. He would go and ask children if he could play and invariably they would say no.'

However, problems keeping up with work were also noted:

> 'She's very slow so she can't keep up with it all. So it got to the stage where she was having to leave it, so it used to upset her a lot.'

Eight of these mothers felt that speed of working continued to be a problem for their child and they were therefore having difficulty keeping up with their peer group, which both mother and child felt was disheartening.

CURRENT SCHOOL ATTENDANCE

The majority of children (n=31) were reported to be fit and well by their mothers, missing up to 5 days a year from school due to illness, or routine hospital appointments. However, a substantial number (N=9) were still having regular days off because of headaches or tiredness. For these children having a cold or minor illness often led to symptoms that lasted for longer than might be expected, culminating in a week or more off school:

> 'What I find now, when he is ill, if he's got a cold, it really knocks the stuffing out of him. Whereas his sister would maybe have a cold for a day or two, he's out for the whole week'

Seven of these nine children were also those missing the most school because of hospital appointments: Six children who were seeing other health care professionals including speech therapists, orthoptists, audiologists, endocrinologists and physiotherapists were missing at least one day a month from school; whilst one child who was seeing several different specialists was missing 6 to 7 days a month from school because of hospital appointments. In addition one child had missed 4 months of school because of exclusions for behaviour problems.

SOCIAL FUNCTIONING

Almost half the mothers (N=17) said their child was socially isolated. Mothers of 10 of these children suggested that this was because of something in the child's own behaviour – peers had tried to engage with the child but met with resistance, or even aggression and so gave up. Three mothers felt their children had been bullied or picked on because of the cancer. For a further 10 children social relationships were reasonable, though more limited than they had been in the past. Ten children were reported to be having no problems with peer relationships, with friendships having stayed the same or even become closer. In addition, both mother and teacher ratings of the SDQ subscale 'Peer Relationship Problems' indicated a higher prevalence of relationship problems than would be expected in a community sample (see table 4). Mothers' ratings also suggested a higher prevalence of Pro-social Behaviour problems, whereas teachers did not.

BEHAVIOUR PROBLEMS

Thirteen mothers described their child as having behavioural problems including being short tempered or aggressive. This was often linked to episodes of frustration at not being able to do tasks properly or as quickly as others. One of these children also had a diagnosis of ADHD. However, whilst mothers' scores on the conduct problems subscale of SDQ suggested these children displayed more behaviour problems than would be expected in a community sample, teacher ratings were similar to those of population norms. Mothers' ratings of hyperactivity/inattention were also higher than norms, unlike those of teachers (see table 4).

EMOTIONAL FUNCTIONING

Seventeen children were described by mothers as having emotional difficulties. Four were said to be withdrawn, 9 as frequently miserable and down and 4 were described as worriers. This latter group of children worried about most things including school

performance, health and the future. However, their biggest concern seemed to be a fear of being ill again. Both mother and teacher ratings of Emotional Symptoms indicated higher prevalence of emotional problems than would be expected in a community sample (see table 4).

DISCUSSION

Although the majority of our sample was in mainstream school, over three-quarters of the group had been identified as having SEN. Literacy and numeracy were the most commonly recognized areas of educational attainment requiring improvement; of the children with an IEP over half had progress in literacy and more than one quarter had numeracy as a goal. Cognitive testing confirmed literacy as an area of weakness, but also identified limitations in verbal and performance IQ, memory, attention/concentration and learning. Like literacy and numeracy scores, verbal IQ scores reflect prior knowledge and weakness in these areas is likely to reflect the limited school attendance experience by many of these children. On the contrary, lowered performance IQ, memory, attention/concentration and learning indicate core cognitive deficits which will further undermine these children's success in the classroom.

The problems shown by the children in terms of performance IQ, for example, could contribute further to problems with academic progress. Performance IQ tasks measure non-verbal abilities including fine motor skills and visual information processing. All these tasks are timed and some allow bonus points for extra fast work. The low scores achieved by the children in our sample therefore indicate that they will be working at a slower pace than their classmates. Furthermore, eight mothers had noted a problem with speed of working on return to school which was holding their child back. This, along with the compromised memory, concentration and learning skills shown by our sample, may compound the difficulties these children already face in closing the curriculum gap and so further exacerbate the difference in knowledge and acquired skills that already exists between them and their peers.

Some discrepancy was seen between children's actual performance on academic tasks such as reading and comprehension and SEN input. This suggests that recognition of LD in this group of children and therefore provision of appropriate remediation is lacking. A further mismatch between performance and remediation was noted for memory problems.

Indeed, whilst the majority of children in the sample had some problems with memory functioning only a few were getting any support for this specific problem. As memory problems are likely to underpin general LD in the classroom, reasons for such a shortfall should be considered. It is possible that provision for literacy problems exceeds that for memory difficulties simply because reading and comprehension are easily measured [Butler and Mulhern, 2005], whilst memory (which is more likely to be an underlying process which influences academic progress such as literacy) is harder to quantify. Concentration/attention was also problematic according to CMS scores. Furthermore, mother scores on SDQ suggested a problem with hyperactivity/inattention. Our CMS test results suggest more children may have benefited from help with memory and concentration and schools should be urged to tackle underlying deficits as well as performance indicators.

Table 4. Percentage of children classified as normal, borderline and abnormal for Parent (PSDQ) and teacher (TSDQ) ratings of SDQ in the community [Meltzer et al., 2000] and current sample of brain tumour survivors

Scale		PSDQ			TSDQ		
		Normal	Borderline	Abnormal	Normal	Borderline	Abnormal
Emotional Symptoms	Community population	80.8	7.8	11.4	91.4	3.8	4.8
	Brain tumour Survivors	24.3	24.3	51.4	51.7	17.2	31.0
Conduct problems	Community population	76.4	10.9	12.7	86.9	4.8	8.3
	Brain tumour Survivors	59.5	16.2	24.3	89.7	3.5	6.9
Hyper activity /inattention	Community population	77.9	7.4	14.7	82.5	4.8	12.7
	Brain tumour Survivors	59.5	18.9	21.6	82.8	3.5	13.8
Peer relationship problems	Community population	78.0	10.2	11.8	87.9	5.1	7.0
	Brain tumour Survivors	18.9	16.2	64.9	75	3.6	21.4
Pro-social behaviour	Community population	95.0	2.7	2.3	73.6	13.3	13.1
	Brain tumour Survivors	83.8	10.8	5.4	75	14.3	10.7
Total difficulties	Community population	82.1	8.2	9.7	81.3	9.2	9.5
	Brain tumour Survivors	43.2	13.5	43.2	71.4	7.2	21.6

Furthermore, the difference in verbal and visual memory skills indicated by our results should be noted. Any deficit in immediate verbal memory is likely to have far-reaching implications for school-age children, who spend much time engaged in tasks that are dependent on verbal memory; difficulty comprehending oral instructions for example could lead to problems in assignment completion. Anecdotal evidence also suggests that children who have had a brain tumour often appear not to be listening and simply can not remember what they have been told, suggesting that concentration/attention difficulties may also underlie verbal memory problems.

Mothers described problems with social and emotional functioning and on SDQ, both mothers and teachers rated social and emotional problems as more prevalent than in the general population. Previous research has highlighted the risk of social and emotional problems for brain tumour survivors [Lannering et al., 1990; Steinlin et al., 2003; Carpentieri et al., 2003]. These deficits have been suggested to have a neurological basis, as children with brain-related chronic health conditions such as epilepsy and cerebral palsy, display more

social problems than children with non-brain-related illness. Although the mechanism connecting cognition and social behaviours is as yet unclear, attempts to define a direction of effect have been made; Nassau and Drotar [1997], for example hypothesize that children with CNS-related chronic health conditions such as cerebral palsy and epilepsy, demonstrate deficits in social competence and peer relationships because cognitive impairments hinder the understanding of social cues and social relations.

However, whilst a direct brain-behaviour relationship would seem to provide a likely explanation for the psychosocial difficulties shown by children with a CNS tumour, the evidence is not clear-cut. Glazebrook, Hollis, Huessler, Goodman and Coates [2002] for example, demonstrated that whilst children with neurological problems were the group most vulnerable to emotional and behavioural disturbance, children with non-neurological chronic disease also showed an increased prevalence of such problems compared to population norms. This suggests that there are other factors associated with childhood illness, which may also be impacting on the mental health of children with brain dysfunction. Indeed, being diagnosed with any chronic illness is likely to prove to be a upsetting event; being diagnosed with a life-threatening illness is undoubtedly even more traumatic and must therefore be viewed as a stressful event, which will impact upon a child's adjustment. Parent's descriptions of the difficulties experienced by children on return to school provides further evidence of the adjustment problems experienced by children.

Furthermore, other interpretations of the evidence of the association between LD and both social and emotional difficulties have been given. It has been suggested for example, that pressures of the curriculum impose increasing strains on children with LD leading to feelings of intellectual inadequacy and sadness, which can in turn erode self esteem [Levine et al 1992]. This can make it harder for the child to get along with other children and to keep friends. It has also been suggested that children with specific LD often become angry and frustrated, leading to problems with behaviour [Abrams, 1986]. Indeed, co-morbidity of LD and conduct disorders has been consistently demonstrated [e.g. Meltzer et al., 2000]. It has been suggested that failure experienced by students with LD may result in excessive anger, which then leads in turn to misbehaviour [Abrams, 1986].

It is perhaps not surprising therefore that the children in this study were described as having behavioural problems including being short tempered. This was usually seen by mothers as a response to performance failure. However, whilst mothers rated behaviour problems as higher than would be expected from community norms, teachers rated them as similar to population norms. Discrepancy between mother and teacher ratings of behaviour problems has been noted elsewhere [Achenbach, McConaughy and Howell, 1987] and it is possible that differences in mother and teacher ratings reflect actual differences in behaviour in different social contexts. However, other explanations are possible. Firstly, mothers and teachers may have different expectations and tolerance of behaviour. Secondly, in a classroom situation with more than 20 children to attend to, behavioural problems such as getting cross when unable to do a task may go noticed. Likewise differences in ratings of hyperactivity/inattention may also reflect either mother/teacher differences in expectation and toleration, or the 'visibility' of behaviours such as fidgeting and distractibility. Furthermore, teachers cannot be expected to have comprehensive understanding of the implications of a brain tumour for a child's behaviour.

Parental complaints about the difficulties faced in getting support in school for children who have had a brain tumour should also be recognised. In principle, survivors of brain

tumours should be included automatically within their school's SEN support system. In practice, however, this is not always the case. Teachers may be reluctant to initiate the lengthy form-filling required to initiate the procedures (possibly because they fail to distinguish between brain tumour and other serious illness, and thus assume that intellectual recovery will occur in time). Even if a teacher does decide to take action, it is likely that the standard literacy-related support methods are poorly tuned to the needs of CNS tumour survivors. These children may have missed several years of schooling. Consequently, they lack the foundation skills necessary for achievement throughout the school. Despite the obvious fact that children who miss years of school will lack basic skills, as noted in this study many are expected to function in age-appropriate classrooms. Any child who misses so much school will flounder, and even more so those who have poor attention and memory skills, perhaps visual or hearing loss as a consequence of the tumour, and may also be unhappy at school and unpopular with other children. Parents repeatedly complain about lack of school support and teachers' resistance to acknowledge the special needs of this population. Thus there is a clear need for a special programme of rehabilitation and remediation for these children.

IMPLICATIONS FOR REMEDIATION

The LD of this population have been recognised for a long time, and yet there has been no national programme developed to rehabilitate survivors or provide educational support in the UK. The reasons for this are partly historical; survival was once the only goal and 'quality of survival' secondary; partly financial; there are limited educational resources available and children with a potentially life-threatening condition do not necessarily qualify. Perhaps the reasons are also to do with medical training and the historical organisation of the Health Service, geared to heroic medicine and not to long-term rehabilitation.

However, as noted earlier NHS guidance has begun to place greater emphasis on the assessment and remediation of learning and psychosocial problems after brain tumour and it is recommended that:

> 'Healthcare and education professionals should be aware that the treatment of childhood cancer may have an impact on neurological function in later life, particularly if irradiation of the brain occurs at a young age. Regular review of neurological function should be part of normal follow up. If a problem is suspected, the patient should be referred to a psychologist for a cognitive assessment.' [www.sign.ac.uk]

Thus we suggest that children with cancer who have a diagnosis of brain tumour should undergo a cognitive assessment with a standard measure (for instance the CMS) at the start of treatment. The assessment should be repeated annually, to monitor changes over time. We suggest that a comprehensive follow-up service for these children must include:

i) provision of assessment and rehabilitation services for individual children.
ii) information and advice for parents about the management of learning difficulties after treatment, including counseling about realistic expectations and practical guidance.

iii) comparable information for teachers, who are often poorly informed about the strengths and difficulties of children with such medical history. A booklet is now available for teachers and parents addressing these issues [Eiser, Davies and Gerrard, 2004]. This was a consequence of an incidental finding during the study that teachers wanted more information about the impact of a tumour on children's learning and behaviour.

It is clear from this study and research literature in general that reported memory problems are prevalent after diagnosis and treatment of brain tumours. Such problems are closely linked to emergence of learning problems, failure to make educational progress, and future employment problems [Mostow et al., 1991]. However, it is equally clear that, although systematic trials are lacking, interventions to address memory difficulties can be effective in addressing the problems faced by children with acquired brain injuries including brain tumours [Limond and Leeke 2005]. Recent work undertaken in the US, may suggest a starting point for the remediation of these children. Current approaches in the US have drawn on methods to treat children after traumatic head injury. These include cognitive remediation and ecological manipulations.

i) *Cognitive remediation.* The most widely used method draws on principals of brain injury rehabilitation, educational psychology and clinical psychology [Butler and Copeland, 2002]. These include Attention Process Training, meta cognitive strategies and cognitive behavioural approaches. Based on successful reports involving individual patients and case studies, a national intervention is in progress.
ii) *Ecological manipulations* There are arguments that alterations in environmental demands in combination with rehabilitation is most likely to result in therapeutic gains. On the surface, recommendations based on the ecological approach are fairly basic. They can include making modifications to the child's working environment, negotiating additional time for course-work and exams, using true-false or multiple choice formats rather than essays and opportunities to tape record lessons. The use of visual aids to support learning may also be beneficial given the superiority of visual memory in our sample. These ideas could be used as simple recommendations for schools.

FUTURE INTERVENTIONS

Based on our findings during this study, we are proposing to undertake an intervention study with a group of brain tumour survivors. The philosophy underlying our proposed assessment and rehabilitation service is based on principals of sound neuropsychological assessment and rehabilitation [Wright and Limond 2004; Limond and Leeke 2005]. The framework for rehabilitation will utilise published frameworks targeting prospective memory tasks (e.g. content free cuing, [Manly et al., 2004] ; neuropage [Wilson, Scott, Evans and Emslie, 2003; Manly et al., 2004]). These interventions will utilise both randomly presented content-free cue (e.g. vibration from a pager or mobile phone) to prompt a child to focus on and rehearse a future plan e.g. "when I get home I will pass on a letter to my mother", or will

include a specific task related cue, such as the text message, "when you get home you need to pass on a message". Cues will vary in their temporal proximity to intended actions e.g. the message "don't forget to take your sports kit today" either presented to a child in the morning or the previous evening.

CONCLUSION

Our findings point to specific LD for brain tumour survivors and a shortfall between these deficits and remediation. These children also exhibit behavioural, social and emotional problems which may be linked to the problems they are experiencing. Compromised learning ability means that survivors will require special help to acquire new skills and information. Slower processing skills mean that these children will also need more time to complete tasks both in class and in tests. Remedial programmes should be developed which are appropriate for the nature and degree of difficulty experienced by these children and the effectiveness of these strategies should be established through intervention studies. Finally, schools need to be aware of the special needs that survivors of brain tumours may have in the classroom.

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Chapter 6

THE USE OF PSYCHOTROPIC DRUGS IN PATIENTS WITH LEARNING DISABILITIES AND EPILEPSY

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ABSTRACT

Many patients with epilepsy have psychiatric symptoms, and recent epidemiological studies from selected clinics suggest that over 50% of patients may have a recognisable psychiatric disorder and receive psychotropic drugs, sometimes, but not always, on account of their psychiatric symptoms. The situation in patients with learning disabilities and epilepsy is similar but diagnostic issues are more complicated and, in many instances, psychotropic drugs are frequently used for unwanted behaviours, such as aggression, but in the absence of a clear diagnosis. The most commonly prescribed psychotropic drugs in learning disabled patients with epilepsy are neuroleptics.

As far as the use of psychotropic drugs in patients with learning disabilities and epilepsy is concerned, pharmacological interactions with the anticonvulsant drugs and seizure precipitation represent the major problems for clinicians.

This review focuses on antidepressant and antipsychotic drug therapy, with some further brief comments about other psychotropic drugs that are used in the management of behavioural problems of this population of subjects. The effect of antiepileptic drugs on behaviour is also discussed in the light of a rational psychopharmacotherapy of patients with epilepsy and learning disabilities.

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INTRODUCTION

Epilepsy is the most prevalent among serious neurological disorders and afflicts 0.5% of the general population (1). The prevalence of learning disabilities (LD) in the general population is approximately similar and both groups of conditions share a certain degree of stigmatisation and a common heritage of heterogeneity (2). Up to a forth of patients with epilepsy have LD and, conversely, up to half of all patients with LD have seizure disorders (3). Moreover, patients with epilepsy and LD, particularly those with more severe disablement, are at additional risk for the development of behavioural problems. In this group of patients diagnostic issues are more complicated, and psychotropic agents are frequently used to suppress unwanted behaviours, such as aggression, but without a clear diagnosis. The most commonly used drugs in LD patients are neuroleptics, which are prescribed for up to 60% of subjects (4).

However, there is very little regarding the use of psychotropic drugs, in the way of controlled studies, and the majority of data come from open studies. Most of them involve patients who do not have epilepsy or have been carried out in population in which the percentage of patients with epilepsy is not well specified.

The aim of this paper is to review the use of psychotropic drugs in patients with epilepsy and LD discussing major problems that clinicians may encompass: drug-drug interactions between anticonvulsants and psychotropic drugs and the seizure risk.

CLASSIFICATION OF PSYCHOTROPIC DRUGS

Antidepressant Drugs

In recent years a number of newer antidepressant drugs have been introduced into clinical practice (Table 1). Essentially these are non-tricyclic drugs and mianserin, maprotiline or viloxazine represent early variants. All these drugs have a complicated metabolisms (Table 2) and some of them have inhibition properties (Table 3).

The Selective Serotonine Reuptake Inhibitors (SSRIs) are represented by citalopram, fluoxetine, fluvoxamine, sertraline and paroxetine. Of these molecules, citalopram is the most selective, inhibiting serotonin reuptake 3,000 times more than that of noradrenaline, and 22 thousand times more than that of dopamine. In general, the SSRIs are well tolerated and safe in overdose when compared with tricyclic drugs.

The latest generation of antidepressants has been developed to derive therapeutic benefits from tailor-made actions at specific monoamine receptor and re-uptake sites, in theory providing better efficacy and tolerability.

Table 1. Brief classification of psychotropic drugs currently available

Antidepressants

Mono-Amino-Oxidase Inhibitors (IMAOs)
Tricyclic antidepressant drugs (TCAs)
Selective Serotonin Re-uptake Inhibitors (SSRIs)
Noradrenergic uptake inhibitors (NARIs)
Serotonin –Noradrenaline Uptake Inhibitors (NSRIs)
Noradrenaline -Selective Serotonin Reuptake Inhibitors (NASSAs)

Antipsychotics

Typical

Phenothiazines and buthyrophenones

Atypical

Benzisoxazoloes, benzisothiazoles, thienobenzodiazepines, dibenzothiazepines and dibenzothiazepine derivatives.

Minor tranquillizers

Barbiturates
Benzodiazepines
Others

Mood Stabilizers

Lithium

Table 2. Cytochrome P450 (CYP) isoenzymes involved in the metabolism of psychotropic drugs

CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4
Antidepressants	**Antidepressants**	**Antidepressants**	**Antidepressants**	**Antidepressants**
Amitriptyline	Sertraline	Amitriptyline	Fluoxetine	Amitriptyline
Clomipramine	Bupropione	Citalopram	Paroxetine	Clomipramine
Imipramine	Fluoxetine	Clomipramine	Mianserine	Desipramine
Trazodone	**Anticonvulsants**	Imipramine	Venlafaxine	Imipramine
Fluvoxamine	Phenytoin	Moclobemide	Trazodone	Norclomipramine
Mirtazapine	**Antipsychotics**	**Anticonvulsants**	Nefazodone	Nortriptyline
Duloxetine	Thioridazine	Mephenytoin	Amitriptyline	Trimipramine
Antipsychotics	Olanzapine	Esobarbital	Clomipramine	Nefazodone
Chlorpromazine		Mephobarbital	Desipramine	Sertraline
Haloperidol			Imipramine	Venlafaxine
Clozapine			Norclomipramine	**Antipsychotics**
Olanzapine			Nortryptiline	Haloperidol
Ziprasidone			Trimipramine	Clozapine
			Maprotiline	Risperidone
			Mirtazapine	Ziprasidone
			Duloxetine	Iloperidone
			Antipsychotics	Quetiapine
			Chlorpromazine	**Anticonvulsants**
			Thioridazine	Carbamazepine
			Haloperidol	Tiagabine
			Olanzapine	
			Risperidone	
			Iloperidone	

Table 3. Cytochrome P 450 (CYP) isoenzymes inhibited by different psychotropic drugs

CYP ISOENZYME	ANTIDEPRESSANTS	ANTIPSYCHOTICS
CYP 1A2	Fluvoxamine Fluoxetine Paroxetine Sertraline	
CYP2C9/10/19	Fluoxetine Sertraline Fluvoxamine	Thioridazine Clozapine
CYP2D6	Fluoxetine Paroxetine Sertraline Duloxetine Clomipramine	Thioridazine Haloperidol Clozapine Olanzapine Risperidone
CYP3A4	Fluoxetine Fluvoxamine Nefazodone	Chlorpromazine Thioridazine Haloperidol Risperidone

Reboxetine is a selective noradrenergic re-uptake inhibitor (NARI) with low affinity for histaminergic, cholinergic, dopaminergic and alpha-1 adrenergic receptors. It appears to be equally as effective as the tricyclics in treating depression, and there is a suggestion that it may be more effective than fluoxetine (5). Venlafaxine is a serotonin-noradrenergic re-uptake inhibitor (SNRI), which is similar to the earlier generation of antidepressants, but it does not

interact with histaminergic or cholinergic receptors, thus diminishing side effects due to those receptor systems. Several studies have indicated that this drug is as effective or even more effective than older antidepressants such as tricyclics (6). Moreover, it seems to have less side effects due to interaction with histaminergic or cholinergic receptors. Another SNRI is nefadazone whose most potent action is the blockade of 5HT2 post –synaptic receptors, leading to a dual mechanism of action on the serotonin system at 5HT1 and 5HT3 subsites. Noradrenaline re-uptake inhibition is only minimal, and there is no interaction with histamine or cholinergic receptors.

Mirtazapine is a noradrenaline-specific serotoninergic antidepressant (NaSSa) and has a selective action at alpha-2 adrenoreceptors, and only at some serotonin receptor sub-types. Its actions increase noradrenergic and serotoninergic transmission by blocking the alpha-2 autoreceptors. However, because it also blocks 5HT2 and 5HT3 receptors, the increased serotonin turnover only stimulates 5HT1 receptors. Thus, it enhances noradrenergic and 5HT1A mediated serotoninergic neurotransmission. It is free of muscarinic, alpha-1 adrenergic and 5HT2 and 5HT3 related side effects, but its effects on histamine receptors can cause sedation and increased appetite. Several studies have shown equal or superior efficacy of this compound compared with other antidepressants (7).

Antipsychotic Drugs

As with the antidepressant drugs, in recent years there have been several new antipsychotic agents introduced into clinical practice. These essentially, with some exceptions, fall into the class of atypical antipsychotics.

The classical neuroleptic drugs, such as chlorpromazine and haloperidol, antagonize dopamine D2 receptors. Their clinical efficacy has been shown to correlate with inhibitory activity at these receptor subtypes. However, these drugs block dopamine receptors also in the striatum leading to unwanted extrapyramidal side effects in treated patients.

The new generation of antipsychotic drugs essentially fall into two categories; those that are clozapine related, which include olanzapine and quetiapine, and other drugs such as risperidone or ziprasidone.

Although clozapine has been available for many years, it was initially not available for clinical use on account of its potential side effect, namely agranulocytosis. However, it has been reintroduced into clinical practice as a model of an atypical antipsychotic. The term essentially relates to the low potential of these compounds to cause extrapyramidal problems, and to have minimum effects on serum prolactin levels. The mechanism of atypicality seems to relate to activity at different receptor subtypes. Generally, the atypical antipsychotics occupy lower levels of D2 receptors than the classical antipsychotics, but one reason for their differing profile may be due to the rapid displacement of these agents from receptors by endogenous dopamine, then thus being more loosely bound to the receptor. The newer antipsychotic agents also have lower relative affinity for striatal D2 receptors as opposed to limbic D2 receptors (dorsal vs. ventral striatum).

THE USE OF ANTIDEPRESSANT DRUGS IN PATIENTS WITH EPILEPSY AND LEARNING DISABILITIES

Studies in this area are scanty and the main data do not specifically address psychopathology in patients with LD and epilepsy. Mood disorders in learning disabled patients are often atypical, with rapid-cycling features, a chronic course and resembling, more often than not, a dysthymia. Therefore, diagnostic issues are extremely complicated, making treatment issues even more difficult. Patients with LD often manifest depressive symptoms in somatization (for instance fatigue or regression) or in dysphoria or sudden sadness, rather than by explicitly saying that they feel depressed.

In general, SSRIs are effective in case of depression, even in the presence of a comorbidity with autism, but some authors have noted the development of emergent-treatment effects, including the onset of hypomanic symptoms, which in fluoxetine studies occurred in 25% of the population investigated (8). Benzodiazepines can be considered for short-term treatment of anxiety, although patients with LD can sometimes react paradoxically to drugs of this type.

Pharmacokinetic Interactions Between Anticonvulsants and Antidepressants

In general, AEDs with induction properties such as PB, CBZ and PHT stimulate the metabolism of TCAs, while VPA can increase their plasma levels (9) (Table 4). An open study, investigating the effect of VPA on amitriptyline and nortriptyline plasma levels. showed a significant increase in the mean AUC for the sum of nortiptyline and amitriptyline (10).

In a case series of 13 patients with major depression, the effects of CBZ on imipramine and desipramine serum concentrations have been investigated (11). The authors demonstrated that CBZ affects not only the metabolism of these drugs but also their protein binding, leading to a significant increase in the free fraction. Because of this phenomenon, the authors suggested that a modification in imipramine dosage regimen does not seem to be necessary in clinical practice.

The influence of fluoxetine on CBZ plasma levels are contradictory and still based on two old studies. The first one is a formal pharmacokinetic study using healthy male volunteers and the authors observed a slight increase in CBZ AUC levels and a decrease in 10, 11-CBZepoxide AUC (12), while the second study is a small series of eight patients with epilepsy that showed no modifications in CBZ plasma levels before and after fluoxetine administration (13). However, these two studies are not comparable because the activity of CYP enzymes is influenced by different factors namely age, sex and ethnicity.

The inhibition properties of several SSRIs on phenytoin metabolism have been tested in an in-vitro study with human liver microsomes (14). The risk for a phenytoin-SSRI interaction seems to be higher with fluoxetine and less likely with the others (paroxetine and sertraline).

A single blind, placebo controlled, crossover trial on kinetic interactions between paroxetine and CBZ, VPA and PHT showed no change in plasma concentrations and protein binding of the anticonvulsants (15). However, studies of paroxetine plasma concentrations are

lacking, but the major enzymatic pathway is a non-inducible enzyme (CYP2D6), making modifications in its plasma levels unlikely, when coadministrated with inducers.

Leinonen et al. (16) observed an increase in citalopram levels when CBZ was substituted with oxcarbazepine in two patients, demonstrating a significant induction effect of CBZ on citalopram metabolism.

Table 4. Pharmacokinetic interactions between antiepileptic and antidepressant drugs

Fluoxetine		=↑		↓		↑				
Paroxetine		=		=		=				
Citalopram	↓	=		=*		=*	=*	=*		=*
Sertraline	↓	=				↑=				
Fluvoxamine		=				↑				
Venlafaxine		=		=*		=*		=*		=*
Reboxetine	↓	=*		=*		=*		=*		=*
Amitryptiline	↓		↑							
Clomipramine	↓	↑	↑		↓				↓	
Imipramine	↓°		↑		↓				↓	
Desipramine	↓°		↑		↓				↓	
Nortriptyline	↓		↑		↓				↓	
Moclobemide		=								
Mianserine	↓				↓				↓	
Trazodone						↑				
Mirtazapine	↓	=								
Nefazodone	↓	↑								
Bupropione	↓			↑		↑		=		
Viloxazine						↑		↑		
	CBZ		VPA		PHT		LTG		PB	

Symbols on the left are referred to antidepressant drug and on the right to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑ increased plasma concentration, ↓ decreased plasma concentration, = unchanged plasma concentration; *Theoretical data, no clinical studies available; °Dosage adjustments are not necessary

The potential interaction between CBZ and fluvoxamine has been evaluated in a small open study of eight patients with epilepsy in steady state for CBZ and no significant changes in CBZ and CBZ-10,11-epoxide occurred (13). There are no studies of VPA-fluvoxamine interactions.

In literature, two studies investigated possible interaction between sertraline and AEDs with induction properties. A double blind, randomized, placebo controlled study with 30 healthy volunteers demonstrated the absence of any pharmacokinetic interaction between sertraline and PHT (17). The same authors, in a double blind, randomized, placebo controlled study on 14 healthy volunteers, observed no significant effects of sertraline on CBZ pharmacokinetic (18). Bonate et al. (19) demonstrated no drug interaction between

clonazepam and sertraline in a randomized, double blind, placebo controlled, crossover study with 13 subjects.

No clinical studies are available about potential interactions between venlafaxine and AEDs while a randomized, crossover study with 18 male subjects showed no pharmacokinetic interactions between venlafaxine and diazepam (20).

Laroudie et al. (21) investigated kinetic interactions between nefazodone and CBZ in 12 healthy subjects. They observed a significant decrease in nefazodone AUC and an increase in CBZ AUC, demonstrating a potential inhibition property of nefazodone on CBZ metabolism.

Ketter et al. (22) investigated the safety and efficacy of CBZ-moclobemide cotreatment in a double blind study. The combination was well tolerated with no modifications in CBZ kinetics, but they did not assess moclobemide plasma concentrations.

It is well known that AEDs with induction properties determine a significant reduction in mianserin plasma concentrations (23).

The use of bupropion is limited in patients with epilepsy by the high seizure risk. CBZ is a potent inducer of its metabolism, taking the antidepressant plasma concentrations to undetectable levels (24). On the other hand, bupropion has shown marked inhibition properties on VPA (24) and PHT metabolism (25). In a randomized, open label, cross over study with twelve healthy subjects, the kinetic parameters of a single 100 mg LTG dose were not modified by steady state slow release bupropion therapy (26).

Antidepressant Drugs and Seizure Risk

Although the risk of antidepressant-induced seizures is well known, most of the data arise from studies using in vitro technique, animal studies and clinical observations (27). It has been known, since their introduction, that TCAs are more likely to be proconvulsant, leading to seizures, mainly in overdose (28). This observation could suggest that the impact of TCAs on seizures is dose dependent.

Of the non-tricyclic drugs, both maprotiline and mianserin seem to be at the more proconvulsant end of the spectrum (Table 5) while the newer generation of drugs, especially the SSRIs, are considered to provoke less in the way of seizures than TCAs. It is reasonable to speculate that the even newer, more selective drugs, might provoke even less in the way of seizures than the SSRIs, data on these compounds are needed.

The reporting of seizures with all the new drugs in clinical trials is at very low levels, either similar to, or lower than the less convulsant TCAs (29). Among SSRIs, fluoxetine is the most extensively studied drug and it is of interest that some studies emphasized the role of serotoninergic transmission in enhancing the anticonvulsant effects of AEDs (30). In fact, Leander (31) demonstrated, in an animal model of epilepsy, that the potentation of the serotoninergic neurotransmission by fluoxetine can enhance the anticonvulsant potency of PHT and CBZ. Therefore, a favorable pharmacodynamic interaction may be suggested.

Table 5. Risk for seizures with some antidepressant and antipsychotic drugs

High Risk	Intermediate Risk	Low Risk
Antidepressant drugs		
		SSRIs
Buproprion	Amitriptyline	Trazodone
Clomipramine	Imipramine	Venlafaxine
Maprotiline		IMAOs
		Mirtazapine
Antipsychotic drugs		
Chlorpromazine (dose related)		Trifluoperazine
Clozapine (titration and dose related)	Haloperidol	Risperidone
		Olanzapine
		Quetiapine

THE USE OF ANTIPSYCHOTIC DRUGS IN PATIENTS WITH EPILEPSY AND LEARNING DISABILITIES

As with the antidepressants, further work needs to be done with antipsychotic agents in the area of managing patients with LD and epilepsy. Studies carried out are mainly anecdotal and with an open design, though recently, a number of atypical antipsychotics have been used in a more controlled manner in patients with LD without epilepsy (32). In general, the tendency is away from using traditional neuroleptics, to using the atypical antipsychotic drugs, not least for their potential effect on negative symptoms and because of the reduced risk for long-term development of extrapyramidal motor symptoms, which are much less likely to occur with atypical molecules. It is important not to give overly large doses and not to taper dosages up and down, avoiding setting off paradoxical reactions and a variety of adverse effects. Clozapine should be avoided mainly because of difficulties in managing dangerous side effects in this group of patients.

So far, the majority of data published has been with risperidone and a number of studies suggested an improvement in aggressive behavior, self-injury, isolation, suspiciousness and social withdrawal. Particularly, two studies in this area have been performed using a double-blind design and both investigated risperidone (33-34). In both studies the dose range was 1-6 mg/daily and reported a significant improvement in a variety of behavioral endpoints, although they were not diagnosis specific. Sedation and weight gain were the main reported side effects.

Pharmacokinetic Interactions Between Anticonvulsants and Antipsychotic Drugs

Thioridazine is metabolized by intestinal sulfoxidases that are only partially affected by inducers such as CBZ, PHT and PB but some authors reported an increased clearance of thioridazine and mesoridazine (the active metabolite of thioridazine) (35). On the other hand,

thioridazine, as chlorpromazine and prochlorperazine, seem to inhibit PHT, PB and VPA metabolism (36) (Table 6).

Several studies have shown that haloperidol plasma levels decrease by 50-60% after CBZ coadministration, with concomitant worsening of the psychiatric clinical features (37-39). Therapeutic drug monitoring data from 231 patients showed that haloperidol levels were 37% and 22% lower in those who were coprescribed with CBZ or PB respectively (40). Iwahashi et al. (39) observed that serum CBZ concentrations in patients treated without haloperidol were significantly decreased (on average 40%), as compared to those treated with both CBZ and haloperidol but their findings have not been confirmed. In a controlled clinical trial on the effects of CBZ and VPA co-treatment on the plasma levels of haloperidol and on the psychopathologic outcome in schizophrenic patients, VPA showed no significant effects on haloperidol plasma levels and it was associated with a better outcome (41). As far as new AEDs are concerned, TPM showed no clinically significant modifications on haloperidol pharmacokinetic in a formal pharmacokinetic study with healthy volunteers (42).

Table 6. Pharmacokinetic interactions between antiepileptic and antipsychotic drugs

Chlorpromazine	↓	↑		↑		↑		↑		
Thioridazine	↓		↓	↑	↓	↑		↑		
Mesoridazine	↓				↓					
Haloperidol	↓	↑	↓		↓		=		=*	
Clozapine	↓		↓		↓		= ↑			
Olanzapine	↓		↓*		↓*		↑*		=*	
Risperidone	↓	= ↑	↓*		↓*		=			
Ziprasidone	↓		↓*		↓*					
Iloperidone	↓*		↓*		↓*		=*			
Quetiapine	↓		↓*		↓					
	CBZ		**PB**		**PHT**		**VPA**		**LTG**	

Symbols on the left are referred to antipsychotic drug and on the right to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑ increased plasma concentration

↓ decreased plasma concentration

= unchanged plasma concentration

*theoretical data, no clinical studies available

Spina et al. (43) compared the risperidone total active moiety (risperidone plus its active metabolite) steady state plasma concentrations in patients treated with risperidone alone and in patients comedicated with CBZ or VPA, matched for age, sex, body weight and antipsychotic dosage. While CBZ caused a significant decrease in the total active moiety concentrations, VPA (at dosages up to 1200-1500 mg/d) had minimal and clinically not significant effects, suggesting that VPA can be safely used in patients taking risperidone. Notably, a clinical study investigated the relationship between CYP2D6 genotype and CBZ-risperidone interaction, suggesting that the decrease in risperidone concentration might be dependent on the CYP2D6 genotype (44). An open study of eight patients with epilepsy showed a mild increase in CBZ plasma levels during therapy with risperidone 1 mg (45).

Although this interaction seems not to have clinical relevance, it might suggest that risperidone, or more likely its metabolites, could modulate CYP3A4 activity and, interestingly, a different enantioselective 9-hydroxylation of risperidone by CYP 2D6 and CYP 3A4 has been shown (46).

Ziprasidone and perospirone are newly available antipsychotic drugs and there are few clinical studies about their interactions. A formal pharmacokinetic study using healthy volunteers showed a reduction (<36%) in steady-state ziprasidone levels after CBZ prescription, that might not be clinically significant (47).

As far as clozapine is concerned, PHT, PB and CBZ (48-49) cause a decrease in its plasma concentrations. However, CBZ is rarely used in combination with clozapine because of the high risk of hematological side effects. Conversely, existing data on the effect of VPA co-administration are contradictory (50-51). According to some authors, VPA may have a moderate inhibiting effect on the demethylation of clozapine, that is catalyzed by CYP 1A2 and 3A4, but the total disposition of the antipsychotic is characterized by a large interindividual variability, being affected by age, gender, body weight, dose per kilogram, smoking habits and ethnicity (52).

Olanzapine plasma concentrations are decreased by CBZ (53), but the authors did not consider this interaction clinically relevant because of the wide therapeutic index of the drug. Unfortunately, there are no pharmacokinetic studies assessing drug interactions between olanzapine and new AEDs in humans.

Quetiapine is a newly introduced atypical antipsychotic, and clinical data about pharmacokinetic interactions are lacking. PHT seems to induce the metabolism of quetiapine, suggesting that dosage adjustment of quetiapine may be necessary when it is coprescribed with other AEDs inducers as CBZ or PB (54).

Antipsychotic Drugs and Seizure Risk

Historically, antipsychotic drugs have been considered proconvulsants possibly because of their D2-receptor blocking activity. One of the most important issues in prescribing these two types of drugs at the same time is about the effect of antipsychotics on the anticonvulsant effect of AEDs.

To determine the risk for drug induced seizures we can use different approaches: observational studies (case-control studies and case reports), drug induced EEG changes, animal models and in vitro techniques in isolated tissue samples. One of the problems of the recent literature is that most of the studies have been performed on psychiatric patients and, though theoretically correct, it is not known if drug related seizures in non-epileptic patients predict risk in patients with epilepsy, and if different epileptic syndromes have different risks for psychotropic induced seizures.

Generally chlorpromazine and clozapine are considered proconvulsant in epileptic patients. The former only at high doses (1000 mg/daily) and the latter at medium and high doses (>600 mg/daily) (55). Clozapine frequently causes epileptiform EEG changes and seizures in 3-5% of patients treated, even at therapeutic doses. Devinsky et al. (56) observed a mean prevalence of seizures of 2.9% with clozapine, and considering different doses, the prevalence is respectively 1%, 2.7% and 4.4% for doses <300 mg, 300-600 mg or 600-900 mg/ daily. Pacia and Devinsky (57) analyzed only patients without a previous history of

seizures and the prevalence of seizures was respectively 0.9%, 0.8% and 1.5% for the same range of doses of the previous study. Thus, with clozapine this seems to be a dose related phenomenon but probably the role of the titration time and increase of dose is more important (58).

As with the newer antidepressants, there is little information about the effect of atypical neuroleptic drugs on the seizure threshold with the singular exception of clozapine. The latter was known to be proconvulsant from early studies, the seizures seemed to be a dose related effect. The incidence of seizures rises to about five per cent at doses 600 mg, although EEG changes may be recorded at lower doses, these results emerging from patients with schizophrenia, and not epilepsy (55). The seizures are often myoclonic, but can be generalized tonic/clonic, or partial depending on the individual patient. Olanzapine, quetiapine and risperidone demonstrated an extremely low risk of seizures when compared with haloperidol and can be considered safer (55) (**Table 5**).

CONCLUSION

In treating patients with epilepsy and LD, diagnostic instruments should be used to overcome diagnostic difficulties. Controlled studies assessing the effectiveness and adverse effects of antidepressants and neuroleptics in epileptic patients with mental retardation are needed.

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Chapter 7

EVENT-RELATED BRAIN POTENTIALS DURING A VISUAL CONTINUOUS PERFORMANCE TASK IN GROUPS WITH READING DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

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ABSTRACT

Reading disorder (RD) and attention-deficit/hyperactivity disorder (ADHD) are two of the most common neuropsychological problems of childhood. Recent studies indicate that many children have both RD and ADHD and it has been proposed that both conditions can be causally related. The objective of this study was the event-related brain potentials (ERP) recording of ADHD and RD children (8-12 years old) during continuous performance task (CPT), in order to distinguish whether children with ADHD only and RD only demonstrate common or specific deficits in attention and/or inhibition processes measured both behaviorally and electrophysiologically. CPT included five conditions: Go, No Go, Warning, False Go and Frequent stimuli. Behavioral data showed that there were no between-groups differences in hits nor omission or commission errors, but in reaction times to hits control subjects showed significantly shorter times than the other two groups. The electrophysiological results showed that P300 amplitude was larger for Go than for No Go condition in Control and RD groups, but not in the ADHD group. For No Go condition, control group showed higher P300 amplitudes as compared to RD and ADHD. However, the electrophysiological responses of these later groups were different, since ADHD showed larger amplitudes than RD to No Go and False Go stimuli, while RD displayed greater P300 amplitudes as compared to ADHD in Go and Warning stimuli. It is concluded that ADHD children present deficiencies in both the allocation of attentional resources and in the inhibitory processes, while in RD children the main problem is the scarce amount of attentional resources devoted to information processing.

INTRODUCTION

Diagnostic Criteria and Epidemiology of Reading Disabilities and Attention-Deficit/Hyperactivity Disorder

Reading disabilities (RD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two of the most common neuropsychological problems of childhood. RD is considered to affect 4% of schoolchildren, meanwhile ADHD affects 3-7% of them (American Psychiatric Association, 2000).

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 2000) defines the ADHD as comprising three clusters of behavioral symptoms: poor sustained attention, impulsiveness, and hyperactivity. DSM-IV describes three subtypes of ADHD based on the pattern of symptom clusters: 1) predominantly inattentive subtype, in which children have six or more symptoms of inattention, but fewer than six symptoms of hyperactivity/impulsivity, 2) predominantly hyperactive/impulsive in which children have six or more symptoms of hyperactivity/impulsivity, but fewer than six symptoms of inattention, and 3) combined, in which children show elevations of six or more symptoms on both dimensions.

However, why do ADHD children show these symptoms is not yet clear. Early studies found a sustained attention deficit (Douglas, 1972), although the confirmation of such deficit has result elusive (Halperin, 1991). Recently the hypothesis of deficit in executive functions, specifically in inhibitory control has been broadly accepted and many researches have been directed to prove it (Barkley, 1997 ; Schachar, Mota, Logan, Tannock and Klim, 2000).

On the other hand, reading disability or dyslexia is a specific developmental impairment in which reading (accuracy, velocity and/or comprehension) is significantly below from what is expected in subjects, given their age, grade level or average intelligence quotient (IQ). When sensory deficits exist, the cognitive deficiencies surpass it, so they could not be explained solely by this fact (APA, 2000).

The characteristic symptoms distinguishing RD from other disorders are problems related to decoding of words, reading of non-words and problems in spelling. There is a general consensus that symptoms of developmental reading disabilities stem from core deficits in phonologic processing (i. e. Stanovich, 1988; Torgesen, Wagner and Rashotte, 1994; and Wagner and Torgesen, 1987, Wagner, Torgesen, Laughon, Simmons and Rashotte, 1993), although working memory (Fletcher,1985; Siegel and Ryan, 1989; Swanson, 1992, 1993, 1994) and recently, attention deficiencies also has been proposed (Facoetti, 2004).

Recent studies indicate that many children have both RD and ADHD. Barkley (1996), claimed that 19-26% of children with ADHD have at least one type of learning disorder, while Semrud-Clikerman et al., (1992) estimated a comorbidity of 23% between RD and ADHD. Due to its high rate of comorbidity, both conditions have been proposed to be related.

There are few investigations that include simultaneous studies of ADHD and RD trying to discern deficits that could distinguish between these groups or, and if it is the case, specify if exists a common cause in both types of neuropsychological problems of childhood. McGee, Brodeur, Symons, Andrade, and Fahie (2004) contrasted ADHD and RD groups on measures of auditory phonological processes and time perception. They found that children with ADHD showed a significant impairment in retrospective time duration estimation, but no impairment on phonological processing. The RD group showed impairment in phonological

processing, but no impairment in estimation of time duration. They concluded that ADHD and RD are two distinct disorders with separate cognitive profiles, at least in the assessed functions.

Equally, there are works studying ADHD children with some comorbid disorders such as RD. For example Nigg, Hinshaw, Carte and Treuting (1998) studied ADHD children with comorbid oppositional defiant conduct and reading disorders. They found a deficit in ADHD, regardless of comorbid disorders, on effortful neuropsychological tasks. Additionally, boys with ADHD plus RD had specific impairment on linguistic output tasks and concluded that in their clinical sample, difficulties on effortful neuropsychological tasks that require planning or controlled motor output, pertain at least in part to ADHD and are not fully accounted by comorbid conditions.

Willcut, Pennington, Olson, Chhabildas, and Hulslander (2005) summarize four hypotheses that have been proposed by several authors in order to explain comorbidity between RD and ADHD. The cross-assortment hypothesis suggests that an adult with RD is more likely to have a son with ADHD, than it could be expected by chance according to the population base rates of RD and ADHD. The phenocopy hypothesis proposes that a child may appear to be inattentive or hyperactive in the classroom due to frustration elicited by difficulties in reading, rather than as a consequence of the neurocognitive difficulties that are typically associated with ADHD, in absence of RD. The cognitive subtype hypothesis suggests that comorbid RD+ADHD is a third disorder that is due, at least in part, to etiological factors that are distinct from those that increase susceptibility to RD or ADHD alone. Therefore, this hypothesis predicts that the comorbid group should exhibit a different pattern of external correlates that it would be expected based on the additive combination of correlates of each disorder, when they occur separately. The common etiology hypothesis declares the existence of a gene or genes that increases the susceptibility to both disorders.

Event-Related Brain Potentials

An important source of knowledge about psychological and neurobiological bases of reading disabilities and ADHD stems from Event-Related Brain Potentials (ERP) studies.

ERP allow the study of cognitive processing with a high degree of temporal resolution (in the order of milliseconds). ERP can be defined as patterned positive and negative voltage changes on the ongoing electroencephalogram associated to sensory, motor, or cognitive events. Physiologically these voltage changes can be explained by synchronous activities of neuronal populations engaged in information processing of a specific stimulus. These positive and negative voltage changes are called ERP components, which appear with specific time delays related to the appearance of the stimulus that elicited them. These components are named according to their polarity (positive or negative) and their latency calculated from the moment of the stimulus presentation. Thus, N100 or N1 component is a negative peak occurring approximately 100 milliseconds after of the onset of the stimulus; P200 or P2 is a positive component occurring approximately 200 milliseconds after of the stimulus onset, etc.

Early ERP components occurring before 60-80 ms are determined primarily by the physical characteristics of the eliciting stimulus and they have been named exogenous components. In contrast, later ERP components also named endogenous, are highly sensitive to changes in the psychological state of the subject, the meaning of the stimulus, and/or the

information-processing demanded by the task. Endogenous components have been used in investigating the physiological bases of human perception and cognition (Hillyard and Picton 1987).

N100, P200, N200 and P300 are endogenous components that have been related to different phases of information processing showing changes in amplitude and/or latency depending on the psychological demands of the experimental conditions. In general it has been observed that latencies of the P100, N200, P200 and P300 components have a direct relation with task difficulty and reflect the speed at which stimuli are evaluated and categorized (Breznitz and Meyler, 2003). P300 latency has been related to stimulus processing time. Polich and Hine (1996) proposed that its latency may function as a temporal measurement of neural activity underlying the speed of attention allocation and immediate memory operations.

N100 or N1 is a negative component with a fronto-central topographic distribution (Iragui, Kutas, Mitchiner and Hylliard, 1993), related to selective attention (Elbert, 1992; Loveless, 1983; Näätänen and Picton, 1987) and may reflect an early selective process: the comparison of the attended stimulus with the model stored in memory, or some active supervising process that evaluates the arriving of information or the access to memory (Loveless, 1983; Picton, 1988).

P200 or P2 is a positive wave with a maximum peak at the central region (Iragui et al. 1993). Some authors as Polich, Ladish and Burns (1990) and Hillyard and Picton (1987) proposed that P200 is a reflection of sensory function; others (i. e. Oken, 1990) described it as an endogenous component that is sensitive to the attentional demands of the task (Johnson, 1989). Moreover Dunn, Dunn, Languis, and Andrews (1998) proposed that this component may reflect both exogenous and endogenous processing.

N200 or N2 is a negative wave whose topographic distribution depends on the sensory modality of the stimulus (Donchin, Ritter and McCallum, 1978). In case of auditory stimulation, the highest amplitude is observed at vertex and in case of visual stimulus, at preoccipital region (Simson, Vaughan and Ritter, 1977). N200 endogenous component can reflect psychological processes associated to target selection (Donchin et al., 1978), or stimulus classification and discrimination (Han, Fan, Chen and Zhuo, 1999; Näätänen and Picton, 1986; Satterfield, Schell, Nicholas, Satterfield and Freese, 1990). Strong relationship has been reported between N200, task demands (Duncan, Rumsey, Wilkniss, Denckla, Hamburger, and Odou-Potkin, 1994; Johnson, 1989) and selective attention (Satterfield et al., 1990). Iragui et al. (1993) proposed another hypothesis suggesting that N200 reflects a categorization process when decisions have to be taken. Moreover, it has been suggested that changes in N200 amplitudes with age may indicate maturation of the stimulus discrimination process, which is traduced in improvement in task performance (Barry, Johnstone and Clarke, 2003).

P300, P3 or P3b is a positive endogenous component with maximum amplitude occurring between 300-600 ms poststimulus at centroparietal scalp sites (Polich, 1993). Several conditions affect P300 amplitude, including stimulus probability and subject's expectations about event probabilities (Johnson, 1986). Less probable events elicit larger P300s. Task relevance of the event also affects P300 amplitude. A theoretical interpretation of P300 is that it indexes activities required for the maintenance of information in working memory, reflecting processes that occur when mental model (or schema) of the environment is refreshed and updated (Donchin, Karis, Bashore and Coles, 1986). Studies revised by Polich

(1999) have indicated that P300 amplitude is directly proportional to the amount of attentional resources employed in a given task and it is associated with a better memory performance. On the other hand, the P300 latency has been proposed to be an index of stimulus evaluation time and is considered as a metric of stimulus classification speed, generally unrelated to response selection process and it is independent of behavioral reaction time and reflects individual cognitive capacity in both normal and patient populations. Moreover, P300 latency is negatively correlated with mental function in normal subjects, shorter latencies are associated with superior cognitive performance (Polich, 1999).

Whereas P300 elicited by Go stimuli (target) has the expected maximum amplitude at the most posterior scalp sites, the No-Go response according to Tekok-Kilic, Shucard and Shucard (2001), has somewhat longer latency and more frontal-central distribution and is often referred to as the No-Go P3 in order to distinguish it from the classical P300. Topographical differences between Go and No-Go conditions have led to the hypothesis that there are two separate components (Go and No-Go) that represent different neural generators and these components are produced by functionally distinctive brain structures. The No-Go P3 has been associated with response inhibition and P300 for Go condition has been related to target detection or response production.

EVENT-RELATED BRAIN POTENTIALS IN READING DISORDERS

Although there exist numerous ERP studies realized on RD children, it is difficult to compare directly their results due to the important methodological differences among them. The authors used different instruments to asses the grade of reading deficits as WRAT, the Boder Test of Reading/Spelling Patterns or some other local tests. Also, the selection criteria of RD subjects vary from 1 to 2.5 or more years of backwardness in reading. Types of stimuli (tones, figures, words, numbers, etc.), modality (auditory or visual), task (active or passive) and the degree of effort required to execute the tasks used in the works have varied in each one of the studies (Duncan, et al., 1994).

The first ERP studies in RD children focused principally in early components (Brying and Järvihleto, 1985; Conners, 1971; Pinkerton, Watson and McClelland, 1989; Preston, Guthrie, Kirsch, German and Childs, 1977; Preston, Guthrie and Childs, 1974; Shields, 1973; Weber and Omenn, 1977) and showed lower amplitudes and/or longer latencies of N100, P200 and N200 components, as compared with normal children.

Subsequent studies interested in ERP, both early components and P300 have thrown inconsistent results. Stelmack, Saxe, Noldy-Cullum, Cambell, and Armitage, (1988) contrasted their findings with previous results on early components and found greater P200 and no P300 differences in a group of 7 poor readers PR compared to 10 normal readers (with mean ages of 9.2 years for the PR and 8.3 years for the control group) during a word-recognition memory task. In the same way, in two papers using auditory and visual oddball tasks Bernal, et al. (2000; 2004) studied normal control and poor readers children (boys and girls) with age range of 10 to 12 years old and average IQ. They observed higher P200 amplitude to auditory and visual stimuli in poor readers than in the control group and P300 amplitudes to auditory stimuli of the same size in PR and in controls to both frequent and infrequent stimuli. The authors concluded that higher P200 amplitude in PR may reflect that

these children paid more attention to both kinds of stimuli (target and non-target) in early stages of information processing in contrast to normal readers who displayed properly more attentional resources in those stages that correspond to evaluation of stimuli. Nevertheless, they argue that these results also may be explained by gender effect, as they observed that girls had greater voltages, as compared to boys.

Segalowitz, Wagner and Menna (1992) did not find differences between RD and control groups in P300 amplitudes or latencies to low probability target sounds of 1000 Hz in an oddball paradigm. Recently Silva-Pereyra et al. (2003) reported similar findings studying control an PR groups in two classification tasks (figures of animals-non-animals and reading words of the same category) finding larger P2 amplitudes during words and figures tasks in PR than the control group. Moreover, their PR showed longer P2 latencies than controls during the word task and for non-animals category. They did not find differences in P300 amplitude between groups, but observed a prolonged P300 peak latency in the word classification task for the RD group.

Studying dyslexic adults and control subjects Rüsseler, Johannes, Kowalczuk, Wieringa and Münte (2003) did not find group differences in P300 for deviant stimuli in active oddball tasks, although they observed an enhancement of P300 amplitude with frontal distribution for standard stimuli. These findings were interpreted as deviances in allocation of attentional resources in dyslexic readers.

Other studies have revealed different results, thus Dainner et al. (1981), and Lovrich and Stam, (1983) have found lower amplitudes and/or longer latencies of P300 and other components occurring before 300 ms in children with reading difficulties. These authors have concluded that dyslexics have deficits in information processing. Taylor and Keenan (1990) compared ERP components in dyslexic and control samples from 7 to12 years old. Visual nonverbal and verbal stimuli were employed and dyslexics showed longer P300 and N200 latencies for language stimuli as compared to controls, as well as smaller P300 amplitudes than control children, during the most difficult lexical tasks. In addition, Erez and Pratt (1992) - using pure tones and two nonsense monosyllables - reported decreased P300 amplitudes at midline leads in subjects with dyslexia and longer P300 latencies in response to nonsense monosyllables in dyslexics as compared to normal ones. Smaller P300 amplitude in RD has been related to either decreased availability of attentional resources or to an inability to allocate them appropriately. Duncan et al. (1994) proposed that altered P300 is a reflection of immaturity of the brain that impairs those cognitive processes that are necessary for a successful reading.

In opposite sense to the findings described before, Barnea, Lamm, Epstein and Pratt (1994) observed larger P300 amplitudes in RD children than in a control group, using a paradigm similar to Sternberg's (1966).

We might resume that PRE results in RD samples are not conclusive: some investigators agree that RD have smaller amplitudes and longer latencies, while others point out that amplitudes are the same in RD versus control subjects. Moreover, some studies show the opposite pattern with greater P300 in the RD children.

EVENT-RELATED BRAIN POTENTIALS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The ERP research in ADHD has focused in examining attentional and executive processing, finding alterations in different stages of the information processing. P300 and its associated components (N100, P200 and N200) are the most studied in ADHD children and although there is certain grade of consistency in the results, contradictory findings also exist. We will review the studies that used selective attention, oddball (Go-NoGo) and Continuous Performance Tests (CPTs) paradigms, which are the most used in ERP research. These tasks are used to study affected processes in ADHD children i.e. attention and inhibitory deficiencies.

Continuous Performance Tests (CPT) involve a rapid presentation of stimuli, where subjects have to respond before designated targets (Halperin, 1991). Tasks duration varies, but it is intended to be sufficient to measure sustained attention, generally lasting from several minutes to a half hour. CPTs had several varieties, regarding to modality (i.e., visual or auditory), stimulus type (i.e., letters, numbers, figures, tones, etc.); and task nature task. For some CPTs, subjects respond to a single stimulus, while in others the target is designated as a sequence of stimuli. Most CPTs differ from the Go-NoGo paradigm in that the nontarget (or NoGo) stimuli may be variable (Riccio et al., 2002). The CPT-AX is a kind of CPT that includes the presentation of a stimulus sequence (letters). Subject's task is to press a button if the letter A is followed by the letter X (A-X sequence = target). When the letter A is followed by another letter (AnotX sequence = nontarget), the subject has to refrain from pressing the button (has to inhibit the motor response). CPT-AX is particularly advantageous, not only for the measurement of inattention, but also for the measurement of response inhibition. It is possible that several variants employed in CPT may measure different aspects of attention or other functions. However, two types of errors are typically analyzed in the CPT: 1) misses, or omission errors, which are considered to be a measure of inattention; and 2) false alarms, or commission errors, which are considered to be a measure of impulsivity. Reaction times (RT) to hits are less common measures.

CPT studies with ADHD patients (Epstein et al., 1993; Losier, McGrath, and Klein, 1996) confirm poorer CPT performance in ADHD children compared to normals, as measured by omission and commission error rates. However, some studies have not found group differences (McGee, Brodeur, Symons, Andrade, and Fahie, 2004) thus, controversy prevails as to whether CPT performance differentiates ADHD from other psychopatologies.

In a review of the literature related to ERP studies in ADHD children, Barry et al. (2003) showed that, in general, studies with oddball tasks have found reduced N200 amplitudes to target and standard stimuli in ADHD children, as compared to normal children. The interpretation on N2 reduction to standard stimuli includes dysfunction in discrimination of task-relevant stimuli and a state of underarousal and/or atypical activation of stimulus discrimination process. In relation to P200 in ADHD, the same authors found higher P200 amplitudes to target and/or standard stimuli in ADHD than controls, which was interpreted as an atypical inhibition of further processing of the sensory input. Higher P2 amplitudes to standard stimuli were attributed to the fact that this type of stimuli are processed without competition in the response-elicitation stage.

In both auditory and visual modalities, posterior target P3 amplitude is tipically reduced in ADHD subjects (Barry et al., 2003). In order to confirm this finding, recently Ozdag, Yorbik, Ulas, Hamamcioglu and Vural (2004) studied a group of ADHD children and a healthy control group in an auditory oddball task observing smaller P300 amplitudes in ADHD.

Various types of CPTs have been used in ERP studies. Most of them have focused on the P3 component elicited by infrequent targets (oddballs). Most common finding in ERP studies of ADHD children, employing CPTs, is impaired target processing, manifested in attenuated P3 amplitudes in response to targets presented during oddball tasks (Klorman, 1991). In a CPT-AX task, Overtoom et al. (1998) found higher inattention scores (omission errors) in ADHD children than in controls and smaller parietal positive waves at the approximate latency of 300 ms to target stimuli, which was interpreted as a sign of less attention in ADHD. No differences were reported in impulsivity measures (comission errors) nor in N2 wave, which is generally seen as reflecting inhibition. Thus, the authors concluded that ADHD group showed deficits in attention, but not in impulsivity (or inhibition).

Selective attention tasks are another type of tasks utilized in ERP studies of ADHD. In these tasks a channel should be attended while another should be ignored, but there also are several varieties, i.e. in some studies a sensorial channel should be attended, in others it should be ignored (Jonkman et al.,1997), while in others the instruction is to attend only one attribute of the stimulus as color, figure, tone, etc. (Jonkman et al., 2004).

Jonkman et al. (1997) in auditory and visual selective attention tasks found that ADHD children had less correct detections and smaller P300 peaks to nontarget stimuli. They concluded that since P300 amplitudes to hits were not smaller in ADHD subjects, it could not be stated that target processing is inefficient in these children. Barry et al. (2003) reported several studies showing reduced auditory P3 amplitude to attended target stimuli in hyperactive, as compared to control subjects. Recently, Jonkman, Kenemans, Kemmer, Verbaten and van England (2004) reported findings on deficiency in the early selective attention around 200 ms, indexed by a smaller frontal positive activity in ADHD children, but they did not observe changes of N200 component.

Interpretations of P300 reduction include abnormal capacity allocation (Frank, Seiden, and Napolitano, 1998), an attentional deficit (Johnstone and Barry, 1996), a context or short-term memory updating deficiency (Johnstone, Barry, and Anderson, 2001), and deficit in memory-related processing (Satterfield, Schell, and Nicholas, 1994). In the same sense, in a task that combined visual, auditory and novel auditory stimuli, Gumenyuk, et al. (2005) reported that the novel sounds elicited a biphasic P3a, where the early phase had smaller amplitude in ADHD and the late phase a larger one in ADHD, respect to controls. The authors interpreted these findings in the sense that ADHD showed deficient control of involuntary attention that might explain their distractibility.

Satterfield, et al. (1994) recorded PRE from six years old ADHD and control boys during visual and auditory selective attention tasks and found that control children presented enhanced N2 and P3 amplitudes (as compared to the responses to non-attended stimuli), when they paid attention to the stimuli in any given modality, while ADHD children has only enhanced P3 in response to visual target stimuli. Auditory N1, N2 and P3 and visual N2 amplitudes to attended target stimuli were significantly reduced in ADHD subjects as compared with normal ones. They interpreted these results as a deficit in cognitive processes essential for the discrimination of novel or important stimuli (as reflected by small N2

responses) and deficits in cognitive processes thought to be crucial to memory and learning (as reflected by small P3 responses) in young ADHD boys.

P3 latency analysis has also thrown contradictory findings. In a study carried out by Winsberg et al. (1993), significant differences were found in P3 latency to target stimuli between 10 years old ADHD and control children, with longer latency in ADHD subjects than controls, although it was clouded by the ADHD being treated with placebo. More clear results were presented by Ozdag et al. (2004) who observed longer P300 latencies in ADHD than in controls. In the opposite sense, in selective attention tasks it was reported that P3 latency to target tones was shorter in 13 years old hyperactive subjects than in controls (Loiselle, Stamm, Maitincky and Whipple, 1980). However, Holcomb, Ackerman, and Dykman (1986), Johnstone and Barry (1996), and Lazzaro et al. (1997) failed to distinguish ADHD subjects from controls based on P3 latencies (Johnstone et al., 2001).

The inconsistencies in these results may have their origin in various factors described previously in this paper about RD children. Some of these factors are related to the modality and complexity of the tasks used, as the results change depending on the degree of effort required to execute them and consequently on the variety of cognitive functions involved.

COMPARISONS OF ERP FINDINGS OF RD, ADHD AND COMORBID GROUPS

In spite of the consensus about the importance of studying the comorbility between RD and ADHD, direct comparisons of ERP between the three groups are scarce. Duncan et al. (1994) studied comorbid groups of LD, ADHD in adult subjects. They compared visual and auditory ERP in a RD group with a history of few ADHD symptoms, another group of RD with many ADHD symptoms, with normal controls, in three tasks of graded difficulty. They observed a shorter N200 latency in the control group with respect to the other two groups, during an easy task of visual modality. For visual P300, only the most difficult task elicited smaller P300 amplitude in the group of RD with many ADHD symptoms as compared to the other two groups. In the auditory modality, RD with many ADHD symptoms group showed larger N200 amplitude than the other two groups. Thus, the authors established that in adults the reduction in P300 in highly demanding tasks, reflected impaired attention and it was associated only with many symptoms of ADHD. Moreover, the finding of larger N200 amplitude in subjects with more ADHD symptoms was interpreted as that these adults allocated more processing resources than the other subjects did, to achieve the same level of performance on tasks.

In children with reading difficulties and in children with attention deficits, longer latencies and reduced amplitudes of N100 have been reported (Loiselle et al., 1980; Pinkerton et al., 1989; Satterfield and Bradley, 1977).

The following are relevant results as report samples of both ADHD and LD groups that were simultaneously studied. In two pioneer papers Holcomb et al. (1985, 1986) recorded ERPs in two experiments: to visual P300 to verbal and nonverbal stimuli and to auditory P300 to tones and to unexpected sounds, in children from 8 to12 years old. They used three clinical groups including reading-disabled, attention deficit disorder (ADD), and attention deficit/ hyperactivity disorder (ADHD) and a control group. The results of the first study

showed significant statistical differences in the overall target/nontarget analysis among the four groups with larger amplitudes in controls than in the three clinical groups. Moreover, ADD and ADHD groups had a smaller P300 effect (target-nontarget), than controls.

Latencies were also different among the groups: controls had the earliest P300 latency followed by ADD, ADHD and RD groups. ERP latency to unexpected stimuli also discriminated ADD and ADHD from controls with shorter latency in control group. Nevertheless, there were not differences in N200 latency or amplitude. The authors interpreted their findings following the Posner idea that conscious attention is the process responsible for the generation of P300 and argued that "the overall amplitude of P300 in all clinical groups is due to a smaller available pool and/or inappropriate allocation of attentional resources". In the second experiment, the authors reported higher P200 amplitude to unexpected stimuli in reading disabled children and in children with attentional deficit with or without hyperactivity in relation with normal control children. They did not report differences between ADHD and RD children.

The overall view of the revised literature let us see the lack of agreement in relation with the deficiencies observed in the clinical groups through PRE paradigms. In the RD group the inconsistencies are more evident, while some researches (Bernal, et al., 2000, 2004, Stelmack, et al., 1988 Silva-Pereyra, et al., 2003, Segalowitz, et al. 1992) report that P300 amplitudes and/or latencies are the same in RD and in normal controls, others (Dainner, et al., 1981; Lovich and Stam, 1983, Taylor and Keenan, 1990, Erez and Pratt, 1992) point out that the RD group has less amplitudes and and/or longer latencies. Finally, higher amplitude in RD in relation with controls has also been reported (Barnea et al. 1994). However, the interpretation of these results is difficult due to the variability in the tasks used to evoke the ERP. On the other hand, in spite of the variety of tasks used, in the case of ADHD group more consistent findings are reported, at least related to P3, where in general smaller amplitude to target is observed in ADHD children, than in control subjects. Nevertheless, due to the fact that the previous studies do not compare RD and ADHD groups simultaneously using the same experimental situation, it is difficult to know if these populations share the same characteristics or they differ in some aspects.

Thus, the objective of this study was to evaluate ERP in ADHD and RD children during CPT, in order to distinguish, whether children with ADHD only and RD only demonstrate common or specific deficits in attention and/or inhibition processes, measured both behaviourally and electrophysiologically and contribute to clarify the etiological relation between these pathologies.

According to Van Leeuwen et al. (1998) an advantage of ERP studies is that they can reveal both specific neurophysiological correlates of poor performance and specific differences in covert neural processing in the absence of performance differences. As described, in ERP studies using CPT, only target ERP has been analyzed, and in some cases an analysis of nontarget stimuli is included. However, a complete analysis of all stimulus categories has not been done. Analysis of the responses to different stimulus categories is very important, as it can provide information about the levels of attention devoted to each kind of stimulus and information about the way in that stimuli with different cognitive demands are processed by children with RD or ADHD, with supposedly different cognitive deficiencies. Thus, the more important stimulus in CPT is the target stimulus that unlike others captures more attention and requires an imperative response. Warning stimulus is important too, though possibly at a minor grade than the target one. Warning stimulus does

not require a response by the subjects, but it could induce a state of higher arousal that might lead the subjects to be in disposition to exert a greater effort of attention. NoGo stimulus requires too, some degree of attention, but in this case subjects must inhibit their response. False Go stimulus is the same as the Go stimulus, except that it appears in a different context, (i.e. not preceded by the warning stimulus). The importance of this stimulus is that it may capture attention due to its similarity with the Go stimulus. Finally, the Frequent stimulus does not require a response by the subject and does not show association with any of the other stimuli. Therefore, it demands minimal attention effort, because of its frequent appearance.

Thus, in the present work a complex CPT was applied to RD and ADHD children, which include five conditions: a) Go (target), b) NoGo (nontarget with warning), c) Warning (the signal that precedes the target), d) False Go (Go stimulus without the preceding warning) and e) Frequent stimuli (those not included in the previous categories).

The combination of complex kind of CPT with ERP methodology is useful to study the relationship between brain function and cognitive operations required in each condition (stimulus type) (Tekok-Kilic, Shucard, and Shucard, 2001).

METHOD

Subjects

Twenty five boys between 7-12 years old participated in the study: Eight boys diagnosed with ADHD but not LD, nine boys diagnosed as LD without ADHD, and eight control boys without ADHD or LD. All participants obtained IQ > 85 on the WISC-R. Written consent to participate in the study was obtained from parents in each case.

Each child of the ADHD group met the DSM IV criteria, as assessed by neurologist´s and neuropsychologist´s check list. Each child was beyond cutoffs on both parent´s and teacher´s forms of the Conners' Rating Scale adapted for Spanish children by Farré- Riba y Narbona (1997) and their scores were less than one standard deviation below control's scores in the decoding reading test of the Neuropsychological Battery for Reading Disabled Children (Yáñez, et al., 2002). Children of the RD group, met the RD criteria according to the DSM IV, they had scores more than one standard deviation below control's scores in the decoding reading test. They did not reach the cutoffs on the Conners' Rating Scale.

Children of the age matched control group were completely healthy. They did not have reading or learning problems of any type.

Procedure

Task

Subjects performed a visual Continuous Performance Task (CPT) of XA type. This task included five conditions: a) Go (target), b) No-Go (non-target with warning), c) Warning (the signal that precedes the target), d) False Go (Go stimulus without the preceding warning) and e) Standard or frequent stimuli (those not included in the previous categories).The stimuli were 600 white drawings of arrows, 3 cm long, pointed to eight directions and presented at

the center of the visual field, one by one in a black background, on a monitor positioned 90 cm from the subject's eyes. The instruction given to children was to press the left mouse key to the second arrow of the sequence of the Go stimulus showed at Table 1, when it was preceded by the arrow pointed out the left. The duration of each stimulus was 50 ms with an interstimulus period of 1.8 –2.5 sec. The probabilities of each type of stimuli are listed in Table 1.

Table 1. Stimuli presented in the CPT paradigm. Underlined stimuli correspond to the category described in the central column and right column shows the presentation probability

Stimuli	Classification	Probability
← ↘	Go	10%
←(→ ↑ ↓ ↖ ↗ ↙ ↘)	NoGo	10%
←(→ ↑ ↓ ↖ ↗ ↙ ↘)	Warning	20%
→ ↑ ↓ ↖ ↗ ↙	Frequent	50%
(→ ↑ ↓ ↖ ↗ ↙) ↘	False Go	10%

Recording

Subjects were seated in a comfortable chair, familiarized with the laboratory settings and in a dark room, when the experimental session started. At the beginning of each session, the children were taught to identify the target stimulus and rehearsed until they were able to execute the discrimination task without errors.

Nineteen electrodes were placed at Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz locations by means of an electrocap, with linked earlobes as reference. A ground electrode was attached to the middle of the forehead. The electrooculogram was recorded from electrodes located below and at the left cantus of the eye, in order to reject trials with eye movement artifact. EEG recordings and stimulation were made using a Neuroscan-Stim System with amplifiers of 0.3-30 Hz of bandwidth. Impedance in each electrode was below 10 Kohms. The sampling period was of 5 ms over a time epoch of 1280 ms with a 100 ms pre-stimulus baseline. Segments with EEG activity higher than 90 microvolts in any derivation were rejected automatically and then revised by ocular inspection (off-line) in order to eliminate segments with artifacts.

Averaging was done separately for responses to each stimulus category (Go, NoGo, Warning, Frequent, and False Go) with a minimal of 15 clean segments, since Taylor and Keenan (1990) have reported that 10-15 segments are enough to obtain a reliable ERP in children.

Only correctly responded trials were included for analysis.

DATA ANALYSIS

Behavioral data

Hits, omission errors, commission errors and reaction time to hits and commission errors were recorded. For statistical analysis frequencies of hits, and errors were converted to percentages in order to make between groups comparisons with ANOVA.

ERP Data

For the analysis of P300 amplitude, nine electrode positions were considered: F3, Fz, F4, C3, Cz, C4, P3, Pz and P4; and for N200 and P200 amplitudes, only six ones: F3, Fz, F4, C3, Cz, C4.

Latency

Latencies of P300, P200 and N200 were determined from grand averages, visually examining ERP to Go stimuli. Latencies of P200 and N200 were measured at Cz at the largest peak in all conditions within the latency ranges of 175-275 ms and 250-450 ms respectively. The largest positive going peak occurring after the P200-N200 complex between 280-700 ms was designated as P300 and its latency was measured at Pz in this interval.

Amplitude

P200 and N200 mean amplitudes relative to pre-stimulus baseline, were calculated for each stimulus condition (Go, No-Go, Warning, Frequent and False Go) and group at the above mentioned leads, within a latency window of 25 ms before and after the highest peak determined in the grand average at Cz. For P300, this evaluation was done within a latency window of 50 ms before and after the highest peak at Pz.

Statistical Analysis

A 3-factor MANOVA was applied to amplitude measures of each component, for each one of the five stimulus conditions separately in the following way: for P300 Group (Control vs. RD vs. TDAH) X Anterior-Posterior electrode placements: frontal (F3, Fz, and F4 leads), central (C3, Cz and C4 leads) and parietal (P3, Pz and P4) X Coronal electrode placements: left medial (F3, C3 and P3 leads) medial (Fz, Cz and Pz leads) and right medial (F4, C4 and P4 leads). For P200 and N200 the same analysis was performed, but for Anterior-Posterior factor only frontal (F3, Fz, and F4 leads), and central (C3, Cz and C4 leads) levels were considered and in the Coronal factor only F3 and C3 for the left medial level, Fz and Cz for the medial level and F4 and C4 for right medial level were considered. Post hoc analysis were

performed with Newman-Keuls Test. For latency measures, between groups comparisons were done at Cz for P200 and N200 and at Pz for P300 by means of ANOVA.

Differences between Go and No Go stimuli for each one of the groups separately, were assessed by a MANOVA with 3 factors: Condition (Go, No Go) X Anterior-Posterior electrode placements: frontal (F3, Fz, and F4 leads), central (C3, Cz and C4 leads) and parietal (P3, Pz and P4) X Coronal electrode placements: left medial (F3, C3 and P3 leads) medial (Fz, Cz and Pz leads) and right medial (F4, C4 and P4 leads).

RESULTS

Behavioral Results

No significant between group differences were found in hits nor omission or commission errors.

Mean reaction time (response latency) to hits was 439 ms (SD 4 ms) in the control group, 528 ms (SD 5 ms) in the RD group, and 518 ms (SD 6 ms) in ADHD group. Significant differences between RD versus controls ($p = .006$) and ADHD versus controls ($p = .015$) were found.

ERP Results

ERPs to Go and frequent stimuli obtained in control, RD and ADHD groups are shown in figures 1, 2 and 3 respectively. It can be observed that all groups presented well defined P2, N2 and P3 components, however P2 and N2 were more clearly observed in frontal and central leads, while P300 was clearly observed in all electrodes. Tipically, P300 was largest in parietal leads and diminished towards central and frontal regions. As can be observed, P300 maxima occurred at 380 ms in Pz for controls, 400 ms in RD and 385 ms in ADHD, however there were no significant between-group differences in latencies. In case of the early components, latencies were more similar between groups than P300 latency. Thus, P200 appeared at 205 ms at Cz for controls, 220 ms for RD and 215 ms for ADHD ms, while N200 latencies were at 205, 220 and 215 ms respectively for each group.

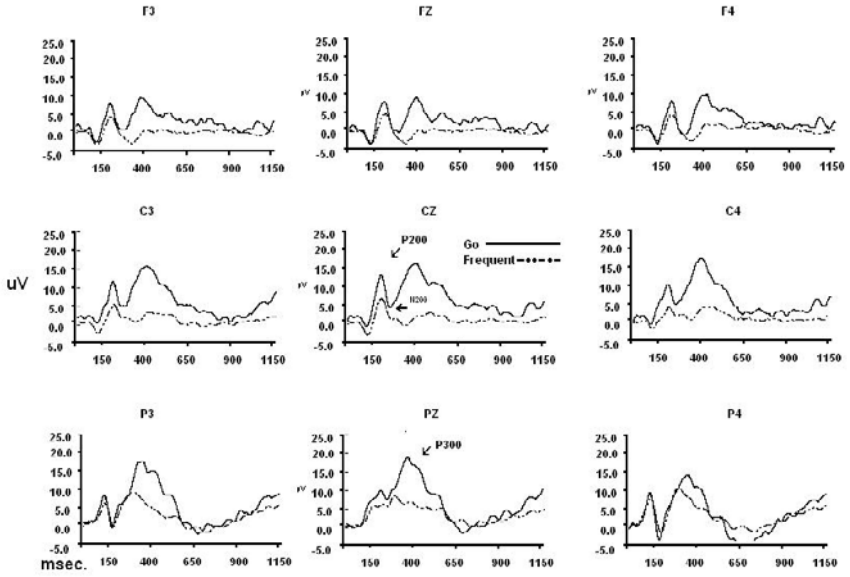

Figure 1. ERP to Go and to Frequent stimuli in the control group at nine electrode locations. P200 and N200 are marked at Cz and P300 is marked at Pz.

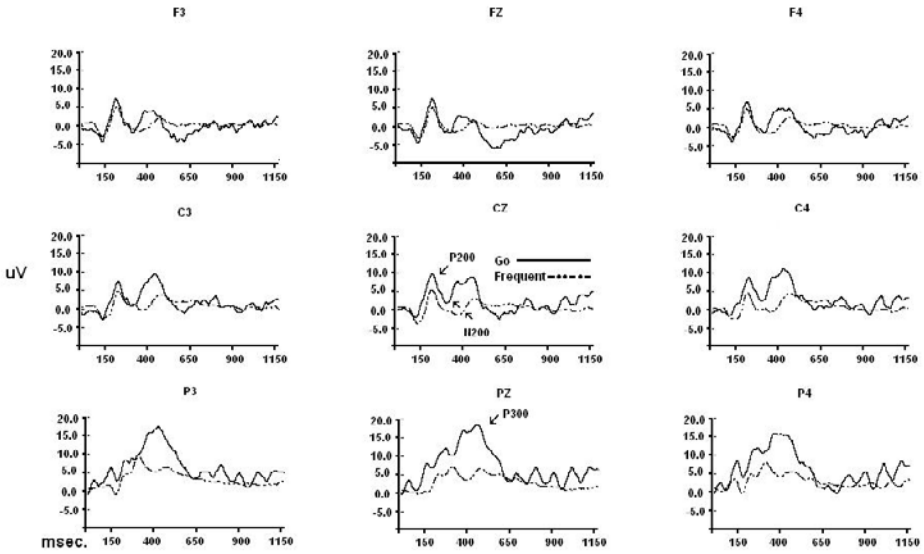

Figure 2. ERP to Go and to Frequent stimuli in the RD group at nine electrode locations. P200 and N200 are marked at Cz and P300 is marked at Pz.

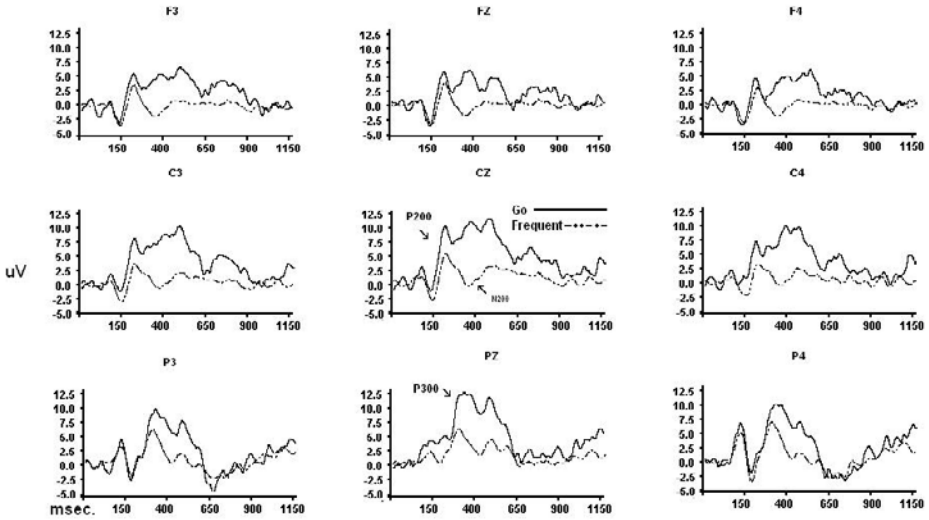

Figure 2. ERP to Go and to Frequent stimuli in the ADHD group at nine electrode locations. P200 and N200 are marked at Cz and P300 is marked at Pz.

Amplitude

We will describe the results obtained for intragroup comparisons first, and then those obtained for the comparison between groups, for each component depending on the stimulus category.

P300 amplitude

Intragroup Comparisons

Comparisons between stimuli category for each one of the groups separately showed the following results: Control group showed a significant effect in the Condition X Anterior-posterior X Coronal interaction (Rao R (4,4) = 7.14 $p<.04$), wherein Go amplitudes were higher than No Go amplitudes; RD group displayed a significant effect in the Condition X Antero-posterior interaction (Rao R (2,7)= 11.25 $p< .006$) pointing out that central and parietal regions in the Go stimuli condition had larger amplitudes than the No Go (mean central = 6.26 vs. 3.34 and mean parietal= 15.62 vs. 5.55, $p<.022$ for Go and No Go conditions respectively). In the ADHD group, there were no differences between Go and No Go stimuli. Thus, it was clear that control an RD groups responded in diifferent manner to both types of stimuli, but ADHD responded in the same manner.

Between Group Comparisons:

Results for between groups comparisons to each type of stimulus (Warning, Go, No Go, False Go and Frequent) were the following:

Go simulus

There was no significant main Group effect, however the Group X Anterior-Posterior interaction was very significant, Rao R(4,42) = 6.35; p<.0004. The Post-hoc analysis (Newman-Keuls Test) showed larger amplitudes for control group respect to RD group at frontal (mean = 8.45μv vs. 2.19 μv; p<.013) region and also larger amplitudes for control than RD and ADHD groups in central leads (means = 16.08μv, 6.96μv and 9.22μv; p<.005 for control, RD and ADHD groups, respectively). Significant greater amplitudes were observed for control and RD than ADHD in parietal sites (mean = 16.64μv, 15.61μv and 9.27μv; p<.002 for control, RD and ADHD groups respectively). Thus, the control group displayed the largest P300 amplitudes respect to the other groups in almost all leads (see Fig. 4).

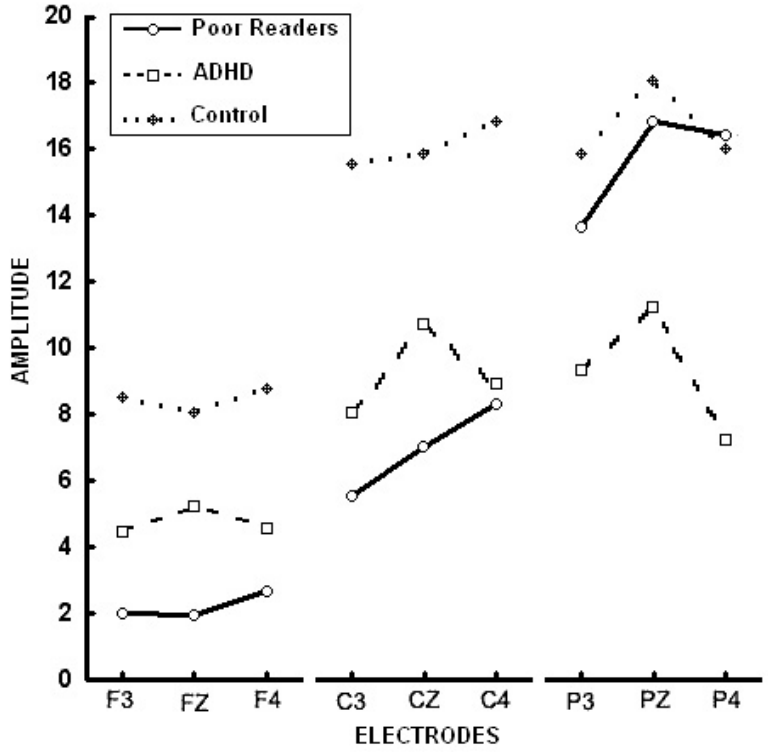

Figure 4. Mean amplitude of the visual P300 to Go stimuli at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 leads for control, RD and ADHD groups. It can be observed that the control group showed higher amplitudes than the RD and the ADHD groups at almost all electrode locations. Moreover, it can be seen that the RD group presented the lowest amplitdes at frontal and central leads.

No Go stimulus

A main group effect F(2,22) = 6.12; p<.0077 was found. Post hoc analysis pointed out significant differences between Control and RD groups (mean = 10.45μv vs. 3.31 μv p<.0006 for Control and RD groups respectively) and Control and ADHD groups (mean = 10.45μv vs. 5.96 μv p<.041 for Control and ADHD groups respectively). Although differences between ADHD and RD groups were not significant, ADHD group showed larger P300 amplitudes for No Go stimulus than RD Group. There also was a significant Group X Anterior-Posterior interaction (Rao R(4,42)=3.17; p<.02). Post hoc analysis showed higher amplitudes for

control than RD group at frontal (mean = 7.55μv vs. 1.05 μv p<.002), central (mean = 12.71μv vs. 3.34 μv p<.0001) and parietal leads (mean = 11.09μv vs. 5.54 μv p<.013); ADHD group showed larger P300 amplitudes than RD children at central (mean = 7.24μv vs. 3.34 μv p<.058), and parietal leads (mean = 9.95μv vs. 5.54 μv p<.050). Furthermore, ADHD group showed lower amplitudes than the control group at frontal (mean = .70 vs. 7.55μv μv p<.002) and central leads (mean = 7.24 vs. 12.71μv p<.01). As shown in Figure 5, it is evident that RD children showed the lowest amplitudes, while control children obtained the higest ones.

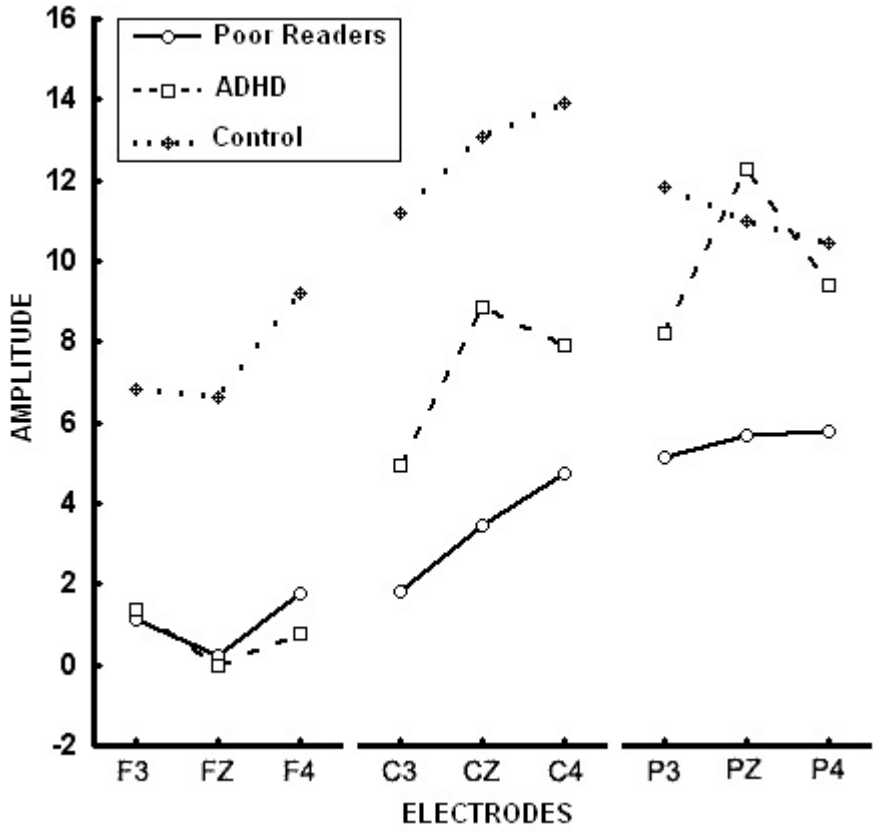

Figure 5. Mean amplitude of the visual P300 to NoGo stimuli at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 leads for control, RD and ADHD groups. It can be observed that the control group showed higher amplitudes than the RD and the ADHD groups at almost all electrode locations. Moreover, it can be seen that the RD group presented the lowest amplitdes at central and parietal leads.

False Go stimulus

In the same sense, that the results obtained to Go and No-Go stimuli, ERP to False Go stimuli showed that control and ADHD groups had greater amplitudes than the RD group, although this effect was marginal (p<.08).

Warning Stimulus

Finally, ERPs to Warning stimuli showed larger amplitudes of control and RD groups as compared to ADHD group. Alhough there was no main effect of group, a significant Group X

Coronal interaction (Rao R(4,42)=4.45; p<.04) and Group X Anterior-to-Posterior interaction (Rao R(4,42)=3.51; p<.01) were observed. Thus, post-hoc analysis for Group X Coronal interaction, showed larger amplitudes for the RD group than the ADHD group at left coronal sites (mean = 4.45μv vs. 2.75 μv p<.055), larger amplitudes for controls than ADHD group at left coronal sites (mean = 4.7μv vs. 2.75 μv p<.04) and at right coronal sites (mean = 5.9μv vs. 2.82 μv p<.04 for control and ADHD groups respectively). However, post-hoc analysis of Group X Anterior-Posterior interaction showed only a tendency to greater amplitudes for RD and control groups, as compared to ADHD children (p<.07 and p<.08).

N200 amplitude

N200 of the early components was the only one that showed group effect in the ERP to False Go stimuli. In this stimulus category, a main Group effect was observed (F(2, 22)=3.81 p<.037), pointed out to larger amplitudes in RD group than the other two groups (means = -3.91 for RD, -1.83 for control and .51 for ADHD groups), however the only significant comparison was between RD vs. ADHD groups.

DISCUSSION AND CONCLUSION

The objective of this work was to compare behaviorally and electrophysiologically groups of control, ADHD and RD children, in order to know if it is possible to differentiate RD and ADHD children based in cognitive processes as attention and inhibitory control, using a CPT. We will focus the discussion on the most significant findings, as an intent to establish this differences.

Behavioral results showed differences between control and RD and ADHD groups. In these measures control children had shorter reaction times to the Go stimulus, than the other two groups, while there were no differences between the RD and the ADHD groups. This finding has already been observed by others authors (Holcomb et al., 1985) and our data confirm the observation that control subjects are faster than both clinical groups for processing of information. Related with this finding, electrophysiological results showed that control group had the highest P300 amplitudes of the three groups, confirming the observation that short reaction times are related to high amplitudes of P300 (Riccio, Reynolds, Lowe, and Moore, 2002). This relationship is important, since these authors have proposed that decrements in vigilance levels are related to increased reaction times. Therefore, it is possible to conclude that RD and ADHD children presented low vigilance levels during the CPT as compared with the control children who presented adequate ones.

Important results were observed for P300, in contrast with early components which did not show differences between groups. It may suggests that the early attentional processes function in the same way in the three groups and therefore the between-groups differences are in the late phases of information processing. This finding are in accordance with those reported by Jonkman, et al. (2004) and Overtoom, et al. (1998).

As mentioned above, warning stimulus is relevant, because it represent the context where the Go stimuli could appear and because it appears with a lower probability than the frequent stimuli. Therefore, this type of stimuli requires attention in order to detect it. The detection of warning stimulus probably generates an arousal state that facilitate the appropriate response

when the Go stimulus appears. In this manner, ERP to warning stimuli showed a significantly higher P300 component in control and RD, than in ADHD children, which can be interpreted as a deficiency of ADHD in the preparation processes to attend the next stimulus and respond adequately.

In the same manner, results also showed higher amplitudes of P300 for the control group respect to ADHD and RD groups in Go condition. However, between controls and RD children, this difference was observed only in frontal and central leads, while in parietal regions control and RD groups displayed the same amplitude, albeit both groups had higher amplitudes than ADHD. In the literature, a number of studies could not find differences between control and RD groups in P300 amplitude or latency (Bernal, et al., 2000, 2004, Stelmack, et al., 1988 Silva-Pereyra, et al., 2003, Segalowitz, et al. 1992); meanwhile others have reported higher amplitudes in RD than controls (Barnea et al. 1994) and on the contrary, some studies found higher amplitudes in controls than RD (Dainner, et al., 1981; Lovich and Stam, 1983, Taylor and Keenan, 1990, Erez and Pratt, 1992). Our results are in accordance with this last position, although the effect was only observed in frontal and central leads and disappeared in parietal regions. One might think that these findings may be due to an insufficient level of arousal generated by the warning stimuli, but this explanation is not adequate, since the P300 amplitudes in response to warning stimuli of RD group were similar to those of the control group. Thus, another possible explanation is that the results may be due to a dysfunction in the generators related with the apparition of P300 in central and frontal leads (i.e. a low synchrony in their activities and /or a minor number of neuronal populations involved).

A more consistent result with those reported in the literature (Ozdag, 2004; Klorman, 1991, Overtoom, et al., 1998, Honkman, et al., 1997, Gumenyuk, et al., 2005) was the effect observed in ADHD group. These children showed lower P300 amplitude than controls at central leads, and in parietal electrodes RD and control groups had major P300 amplitudes than ADHD. Studies revised by Polich (1999) have indicated that P300 amplitude is directly proportional to the amount of attentional resources employed in a given task. Therefore, these results may indicate the possibility that these low P300 amplitudes of ADHD are due to a smaller available pool and/or inappropriate allocation of attentional resources provoked by the low arousal level generated by the warning stimuli in this group. This situation did not facilitate an adequate electrophysiological responses to the target stimuli.

Regarding the main objective of this work, it is important to emphasize the differences found between RD and ADHD groups. The principal difference was that these two groups presented a different pattern in their responses at the different electrode locations as compared to the control group: while at central and frontal leads the two groups maintained lower amplitudes as compared to controls, at parietal leads only the ADHD group had this lower amplitude. If this reduction of P300 is related to attentional deficit (Johnstone and Barry, 1996, Overtoom, et al., 1998), then it is possible that in ADHD this deficit might be more severe, than in the RD group since ADHD group had lower amplitudes in the majority of the electrodes locations.

ERP amplitude to No Go stimuli has been associated with inhibition of response. In the present chapter, this category of stimuli elicited an important response in all groups, mainly at central and parietal regions, but in inferior grade than in the Go stimuli. According to the literature (see Tekok-Kilic, 2001), P3 for No Go stimuli has a more frontal-central distribution in adults, but this distribution was not observed in children of the present study. A

possible explanation is that the P300 topography observed in children might be different from that of the adults due to a maturational process. Moreover, ERP to No Go stimuli, showed a distinct pattern of between groups differences respect to that observed in the Go stimuli. In this category, the control group also presented larger amplitudes in P3 component than RD and ADHD groups, but the RD group showed statistically lower amplitudes than the ADHD group. Moreover, ADHD had major amplitudes in the No Go, than the Go condition; while control and RD children showed the opposite situation. Higher ERP responses to No Go, than to Go stimuli may be interpreted as deficient allocation of the processing resources which might explain the lower amplitudes of ERP of the ADHD children in the Go stimuli. In other words: ADHD inappropriately allocated more resources in the responses to No Go than Go stimuli. In case of the RD group, apparently, the allocation of the resources appears adequate, but it seems that RD do not dispose of sufficient resources in order to respond adequately. It is possible that we could distinguish between ADHD and RD children, according to the characteristics described above.

Following this idea, it is important to note that although the results in False Go stimuli were not significant, a trend of larger P300 amplitudes for ADHD group respect to the other groups was observed, and RD group showed the lowest amplitudes. Apparently, this stimulus type captures involuntary attention of the subjects, probably due to its similitude with the Go stimuli and the ADHD paid more attention to this class of stimuli, than the other two groups did. Thus, it is evident that ADHD children presented problems to allocate their attentional resources, as they paid a greater quantity of attention to stimuli that lacks of importance for the performance of task. The RD group showed the lowest amplitudes in the responses to this type stimulus demonstrating again his low level of attention.

On the other hand, the fact that ADHD had significantly lower ERP amplitudes to No Go stimuli as compared to controls appear to support the hypothesis that this children have a deficiency in the inhibitory control, although this explanation could be applied to RD too.

As a conclusion, we may say that control children presented higher level of attention than ADHD and RD children, in all stimuli type. Moreover, it can also be concluded that in the most important stimuli category as Go and Warning stimuli, ADHD showed lower level of attention, meanwhile the less important stimuli increased significantly ADHD's attention demonstrating their deficiencies in allocation of their attentional resources. A very distinct pattern was presented by the RD group that also showed lower levels of attention than the controls, but more than the ADHD group in the responses to the more important stimulus category and showed the lowest levels of attention to the less important stimulus category.

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Chapter 8

CLASS-WIDE INSTRUCTIONAL FEEDBACK: IMPROVING CHILDREN'S ACADEMIC SKILL DEVELOPMENT

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ABSTRACT

Between 5 and 15% of elementary-aged children in the United States experience difficulties in reading, mathematics, and writing that cannot be explained by sensory deficits, low intelligence, or economic hardship. Moreover, these deficits are closely linked with long-term school failure. The implementation of instructional feedback interventions has been demonstrated to be effective in addressing the range of problems contributing to children's reading, mathematics, and writing difficulties. In this chapter, we describe how instructional feedback can be used to improve children's academic skill development and achievement. We begin by reviewing the current educational progress of students enrolled in public schools. Next, we discuss the importance of implementing empirically-supported practices to improve children's academic skills. We then review the theoretical framework associated with instructional feedback, and provide a rationale for the use of this method with children at-risk for or diagnosed with learning disabilities. Subsequently, we review and evaluate a number of different types of instructional feedback interventions that have been developed for children diagnosed with learning disabilities or learning problems. Finally, we examine recent empirical applications that have attempted to isolate the informational component of instructional feedback with heterogeneous groupings of children.

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INTRODUCTION

The latest reports from the National Assessment of Educational Progress reveal that many children enrolled in American public schools are unable to read, write, and compute. According to these reports, 37% of fourth graders and 26% of eighth graders could not read at the Basic Level (National Center for Education Statistics, 2004a). In the area of writing, 14% of fourth graders, 15% of eighth graders, and 26% of twelfth graders could not write at the Basic Level (National Center for Education Statistics, 2003a). In the area of mathematics, 23% of fourth graders and 32% of eighth graders could not demonstrate proficiency at the Basic Level (National Center for Education Statistics, 2004b). In response to these achievement results, recent reports by the National Research Council (Kilpatrick and Swafford, 2002; Snow, Burns, and Griffin, 1998) and the National Commission on Writing (2003, 2004, 2005) recommended identifying effective instructional procedures that can be applied in classrooms with vigorous effects. These recommendations are consistent with federal efforts to improve our standards for identifying effective practices and advancing our knowledge of evidence-based interventions for children (Eckert, 2005).

In the field of learning disabilities, the number of students diagnosed with a specific learning disability has grown considerably (Keogh, 2002). For example, 2.8 million children between the ages of 3 and 21 years were served in federally supported elementary or secondary programs for students with specific learning disabilities in 2002 (National Center for Education Statistics, 2003b). This figure reflects the largest percentage distribution (44.4%) of children served in federally-supported programs for students with disabilities. Although this percentage has remained relatively constant since 1980, the actual number of children served has doubled (National Center for Education Statistics, 2003b). Similar to the recent educational reform efforts in general education, a number of federally-supported initiatives have been developed to improve the instruction of children with specific learning disabilities (Horowitz and Wendorf, 2003). These proposals have emphasized the need for empirically-supported instructional practices that have been field-tested in classrooms.

Empirically-Supported Instructional Practices

To date, a number of empirically-supported instructional practices have been demonstrated to improve the reading skills of children (National Reading Panel, 2000). Additional practices have been recently examined that involve highly structured and explicit instruction in decoding, word recognition, fluency, and reading comprehension as well as incorporating peer-assisted learning strategies (D. Fuchs and Fuchs, 2005; Williams 2005). Similar advances have been made in the content area of mathematics, including instructional practices focusing on problem solving (L. S. Fuchs and Fuchs, 2005), schema-based learning techniques (Jitendra, 2002), and peer-assisted learning strategies (Fuchs, Fuchs, Yazdian, and Powell, 2002). In the area of writing, only a few instructional skills and strategic processes have been empirically examined, including handwriting and spelling instruction, self-regulated strategy skill instruction, and planning process techniques (Graham and Harris, 2005).

Despite these advancements in our knowledge of effective instructional practice, no single approach has been identified as a universal solution for promoting academic success in all children (Harris, Graham, and Mason, 2003). One meta-analytic review of the effectiveness of various school-based interventions in special education concluded that for any given intervention, the average effect size was exceeded by the variability in that intervention's effects (Kavale and Forness, 1999). As a result, continued effort toward intervention research that incorporates methodologically rigorous approaches that cut across content domains has been promoted (Oxaal, 2005). For example, the National Center on Accelerated Student Learning conducted a multi-site evaluation of the efficacy of writing interventions that targeted transcription skills (handwriting and spelling) and planning processes among struggling writers and children with learning problems (Oxaal). The results from the National Center on Accelerated Student Learning further supported the need for additional research to "identify powerful instructional techniques that are effective with good, average, and struggling writers" (Graham and Harris, 2005, p. 32).

Instructional Feedback: Theoretical Framework

When a child is practicing basic academic skills such as reading, writing, or mathematics, a teacher can provide instructional feedback to help promote the child's learning. The idea that learning occurs when a learner does something and receives feedback is not novel. Providing feedback is a long-standing method of instruction based on E. L. Thorndike's law of effect (Thorndike, 1898, 1911). The main principle underlying this theory is that learning depends on the effect of each response. Later work by Thorndike (1931) demonstrated that providing feedback with practice improved adults' learning to a greater extent than providing practice alone. Subsequent research demonstrated that manipulating the quality of instructional feedback (i.e., right versus wrong) and the duration of feedback (i.e., continuous versus discontinuous) enabled improvements in adults' performance on discrete tasks (Newell, 1974; Trowbridge and Cason, 1932). Although the early theoretical models of instructional feedback emphasized a behavioral mechanism as the method underlying the behavior change (i.e., feedback serves to reinforce the stimulus-response association), more recent empirical and theoretical work has demonstrated that active cognitive processing occurs following the presentation of instructional feedback, causing qualitative differences in what is learned (Anderson, 1993; Singley and Anderson, 1989). That is, a child thinks about the feedback and uses the feedback as information to assist them with learning. Therefore, it is not merely the feedback that changes behavior, but rather the learner's understanding and application of that feedback.

Additional theoretical work has proposed that there are at least five dimensions that can be altered to increase the effectiveness of instructional feedback (Van Houten, 1980). First, the effectiveness of performance feedback can be improved by increasing its *precision*. Biomedical research (Elder, Ruiz, Deabler, and Dillenkoffer, 1973; Whitehead, Renault, and Goldiamond, 1975) has documented the effects of providing immediate, precise feedback on physiological indicators such as blood pressure and skin temperature. It has been argued that providing children with highly precise feedback that is numerically quantified (i.e., number of correct problems) can be helpful for children learning basic academic skills (Van Houten, 1980). Second, the *immediacy* of feedback can have a significant effect on children's

learning. A number of research studies (Hillman, 1970; Trap, Milner-Davis, Joseph, and Cooper, 1978) have demonstrated that immediate feedback is more effective than delayed feedback. Third, the *frequency* of feedback is an important factor to address within the context of the child's stage of learning (Van Houten, 1980). For example, when a child is learning a new skill (i.e., acquisition stage of learning), frequent feedback should be provided in order to strengthen the relationship between correct responding and weaken the associations between incorrect responding. As a child begins to develop fluency, the frequency of providing feedback can be reduced; however, daily feedback should still be provided (McLaughlin and Malaby, 1972; Saudargas, Madsen, and Scott, 1977). Related to frequency is a fourth factor, the *schedule* in which feedback is provided (Van Houten, 1980). Although feedback provided on a frequent or continuous schedule may be important during skill acquisition, feedback that is provided differentially may result in greater increases in performance once a skill has been acquired. Fifth, the *valence* of feedback has been identified as critical factor that can impact the effectiveness of instructional feedback (Van Houten, 1980). Empirical findings have consistently supported the use of positive feedback for improvements in performance (i.e., reductions in erroneous responding or increases in accurate responding) (Fink and Carnine, 1975; Van Houten, Hill, and Parsons, 1975) over negative feedback. Additional instructional factors that have been recently identified (Jiao and Eckert, 2005) include the source of feedback (i.e., teacher, peer, self) and the feedback format (i.e., verbal, pictorial). However, none of these factors has been systematically evaluated.

Despite these theoretical advances regarding our understanding of the mechanisms underlying the effects of instructional feedback, very few empirical studies have systematically examined the effects of classroom interventions that incorporate instructional feedback on children's academic achievement. Although it is routine for teachers to use instructional feedback in their classrooms, we do not know the effects of different forms of instructional feedback (i.e., type, specificity, frequency, duration) on children's academic achievement. As is the case with a vast array of educational interventions that are commonly used in schools today, rigorous scientific evidence supporting instructional feedback interventions to improve educational outcomes has been limited. In the next section of this chapter, we will review and synthesize the existing published studies on instructional feedback interventions in the content areas of reading, mathematics, handwriting, written language, and behavior. An overview of these studies is provided in Table 1.

Table 1. Overview of instructional feedback studies in the content areas of reading, mathematics, handwriting, written language, and behavior

Citation	Participants	Academic Task	Intervention(s)	Results
Conte and Hintze (2000)	18 second grade students in general education (9 boys, 9 girls)	Reading fluency (CBM-R)	Informational performance feedback and goal setting using graphing. Quasi-experimental groups were shown either a dynamic goal line, a static goal line, or none at all (no feedback).	Effect sizes (*d*) showed that the average weekly gain (measured in slope) was greater in the two feedback conditions than in the control condition.
Drabman and Lahey (1974)	1 10-year-old girl	N/A – goal was reduction of disruptive behavior	Every 15 minutes a bell rang and the teacher gave the student a rating (0-10); at the end of the day, the teacher let the student know how many points she earned. ABAB withdrawal design used.	Visual inspection of structured observation recordings showed a reduction in disruptive behavior during feedback phases.
Fink and Carnine (1975)	10 first grade students (4 boys, 6 girls)	Mathematics accuracy	Feedback (a note containing the number of errors made) and graphing of error number. Design was ABAB with no true baseline (A = feedback, B = feedback + graphing).	Statistically significant reduction in errors when graphing was added to feedback.
Pany and McCoy (1988)	18 third graders with learning disabilities and below average reading scores	Oral reading accuracy	Feedback in the form of error correction. 3 conditions: all errors corrected, only errors that caused meaning changes corrected, no errors corrected. Complete within-Ss design where all Ss were in all 3 conditions.	Feedback led to significantly higher accuracy and comprehension; difference between 2 feedback conditions not significant.

Table 1. (cont.)

Salzburg, Wheeler, Devar, and Hopkins (1971)	6 kindergarten students (4 boys, 2 girls, all age 5)	Printing a set of alphabet letters	Intermittent feedback (error correction) and intermittent contingent access to play period, studied separately in a multiple baseline across letters design.	Salzberg et al. conclude that both intervention components worked, but the graphs show much more efficacy for contingent reinforcement than for feedback.
Trap, Milner-Davis, Joseph, and Cooper (1978)	12 first graders (8 boys, 4 girls) in general education	Handwriting (correct cursive letter strokes)	Verbal/visual feedback, rewriting, and potential reinforcement. In a multiple baseline across students ABCD design, a baseline condition came first, followed by feedback, then rewriting was added, and then potential reinforcement was added.	With the addition of each intervention component, handwriting improved both on letters that were being trained as well as generalization letters that were not explicitly trained.
Van Houten (1979)	2 split grade classes: a 2/3 class (29 students) and a 3/4 class (31 students)	Rate and number of different action words	Explicit timing, self-scoring feedback, and public posting. Multiple baseline across classrooms with ABCA format where B was counting all words and C was counting all unique action words. Moreover, students wrote a second story each day without the intervention elements present to observe possible generalization.	The intervention increased writing fluency and action word use, although the expected return to baseline did not occur. Moreover, effects extended to the generalization story.
Van Houten, Hill, and Parsons (1975)	39 fourth graders (2 classrooms with class sizes of 19 and 20) and 19 fifth graders	Writing fluency (for the fourth graders) and completion of language arts exercises (for the fifth graders)	Explicit timing, feedback (by asking students to count how many words were written), public posting, and contingent teacher praise. In the fourth grade classrooms, these components were tested separately in an ABCBCDC design; in the fifth grade classroom they were tested together in an ABA design.	When implemented together, the intervention package substantially increased rate of competing the language arts exercises. When implemented separately, all components increased writing fluency except for praise in 1 of the 2 fourth grade classrooms.

Table 1. (cont.)

Van Houten, Morrison, Barrow, and Wenaus (1974)	36 fourth graders (2 classrooms with class sizes of 15 and 21) and 1 second grade class (no *N* given)	Basic mathematics operations	Feedback (students counted correct answers made in 1 minute), public posting, praise for exceeding past performance. The two fourth grade classrooms constituted a nonequivalent groups quasi-experimental design; the second grade class merely got the intervention.	Students in the intervention groups progressed through skills substantially faster than expected progress and at a faster rate than the control group.
Van Houten, Morrison, Jarvis, and McDonald (1974)	21 second-graders and 34 fifth-graders (2 classrooms of 17 students each)	Composition response rate and development of ideas	Feedback (students counted the number of words written each time), public posting, and explicit timing. Designs used were ABAB (for second grade class) and multiple baseline AB across classrooms (for fifth graders).	Intervention procedures improved both fluency and quality of writing in all 3 classrooms.
Van Houten and Van Houten (1977)	12 EMR students (8-12 years old)	Rate of progressing through reading lab reading lessons	Praise, feedback on how many lessons completed per day, public posting of lesson rate. In a second experiment, peer praise was investigated. ABCAC design with B as posting and C as posting + feedback on the "team" as a whole.	Feedback/posting increased rate of progressing through lessons; posting worked better when team feedback was given.
Willis (1974)	3 elementary school students (aged 9, 10, 11)	Oral reading fluency	Feedback (by counting correct sentence readings) and charting, with praise for "progress." Multiple baseline design across participants.	In all 3 students, intervention substantially increased fluency; in 2 of the students, errors declined substantially.

READING INSTRUCTIONAL FEEDBACK INTERVENTIONS

Willis (1974) examined the effects of feedback on students' oral reading fluency (correct and incorrect sentences read per minute). During baseline sessions, students received only praise for correct sentences; during intervention sessions corrected sentences were rewarded with a green plastic chip and errors were noted by giving the student a red chip. At the end of each intervention session, the chips were counted and the totals were plotted on a graph kept on the wall. The intervention increased the rate of correct sentence reading in all three students, and also reduced errors in two of the three students.

Van Houten and Van Houten (1977) extended the Willis (1974) experiment in a variety of ways: special education students with mild mental retardation participated in the study, the dependent measure was the number of self-paced reading lessons completed per day, and individual and group feedback were compared. Van Houten and Van Houten defined "fluency" as reading 100 or more words correctly per minute, and allowed students to progress to the next reading lesson after demonstrating their fluency on a lesson to an experimenter. Individual feedback was provided in a running tally posted in the classroom containing the number of lessons completed by each student each day of the week; in group feedback, an additional posting of the total number of lessons completed by the entire class was provided on the same chart. Individual feedback was found to increase the rate of lesson completion, and group feedback increased the rate even further.

Pany and McCoy (1988) are somewhat unique in that they provided process feedback to students rather than outcome feedback; these investigators examined the effects of error correction on decoding accuracy and reading comprehension in elementary school students with learning disabilities. Pany and McCoy exposed students to three experimental conditions: no error correction, correction of errors that changed the meaning of the sentence, and correction of all errors. Both error correction procedures reduced future commission of errors on words from both previous and new passages, but had smaller and less consistent effects on reading comprehension. In all cases, total feedback (i.e., correction of all errors) was superior to partial feedback, although these differences did not always reach statistical significance.

Most recently, Conte and Hintze (2000) used standardized curriculum-based measurement procedures (cf. Shinn, 1989) to examine the effects of feedback on oral reading fluency. Students from three general education classrooms served as participants; classrooms were randomly assigned to a no feedback condition, a static goal line condition, or a dynamic goal line condition. In the latter two conditions, students were presented with a graph tracking their performance with either a horizontal line at the top of the graph (static goal line) or a diagonal line drawn from the student's initial reading rate to their future expected rate at the end of the intervention (dynamic goal line). Students in the two feedback conditions increased their fluency faster (as measured by the slopes of their reading rate graphs) than students in the control condition, but differences between the two feedback conditions were small. Effect size calculation estimated the general effect of feedback to be in the medium range.

MATHEMATICS INSTRUCTIONAL FEEDBACK INTERVENTIONS

Van Houten, Morrison, Barrow, and Wenaus (1974) examined the effects of a comprehensive performance feedback package on mathematics fluency in elementary school students. The package included informational feedback (students counted how many mathematics problems were solved correctly per minute), public posting of progress, and praise for exceeding past performance. Students in the classroom exposed to the performance feedback package far exceeded the progress of students in a comparable control classroom as well as expected rates of progress using grade norms. This latter finding was replicated in a second experimental classroom at a different grade level.

Fink and Carnine (1975) also examined the effects of feedback on mathematics performance, but focused on accuracy rather than fluency, and used single-case design elements. In an ABAB design, ten first graders were given informational feedback (a note containing the number of errors that the student made on an arithmetic worksheet) and then feedback plus graphing (in which a graph of the student's error rate per worksheet was posted on each student's desk). During the conditions with graphing, students made significantly fewer errors, although the lack of a true baseline condition or control group obscures an empirical evaluation of the possible utility of feedback without graphing.

HANDWRITING INSTRUCTIONAL FEEDBACK INTERVENTIONS

In the earliest performance feedback study of the present review, Salzburg, Wheeler, Devar, and Hopkins (1971) examined the effects of feedback on the handwriting of six kindergartners. Each day, students were given a handwriting sheet on which to practice printing a selected target letter. After a baseline phase, students entered a feedback phase in which they were given detailed corrective feedback on their printing and then allowed to play outside. After this, a feedback-plus-contingency phase began in which students were required to redo the assignment until a certain proportion of their letters were printed correctly, and only then released to play. Feedback alone did not improve printing quality, but the addition of a contingent play reinforcer greatly improved quality.

Trap, Milner-Davis, Joseph, and Cooper (1978) examined the effects of feedback and other behavioral interventions on cursive handwriting in first graders in general education classes. After a baseline phase, students were given detailed corrective feedback on each written letter, just as in the study by Salzburg and colleagues (1971). However, in two additional phases, the feedback was augmented by a rewriting procedure (students were made to practice writing those letters that had been written incorrectly) and then a "potential reinforcement" phase, in which students were alerted to the possibility of winning a penmanship certificate. With each additional intervention, handwriting improved, and this improvement extended to generalization letters—letters that were not practiced or trained during the procedure. Importantly, unlike Salzburg and colleagues, Trap and colleagues found that feedback alone substantially improved performance.

WRITTEN LANGUAGE INSTRUCTIONAL FEEDBACK INTERVENTIONS

Van Houten and his colleagues conducted several studies examining the effects of performance feedback on written language fluency. In the first, Van Houten, Morrison, Jarvis, and McDonald (1974) used a performance feedback package similar to the package used to increase mathematics fluency in the study by Van Houten, Morrison, Barrow, and Wenaus (1974). This time, the dependent measure was number of words written in ten minutes in response to a writing prompt, and the package consisted of informational feedback (students counted the number of words written), public posting of performance, and explicit timing (students were told that they had only 10 minutes to write). In second and fifth graders, the performance feedback package increased fluency substantially, and also improved writing "quality," as measured by vocabulary, number of ideas, etc.

In a follow-up study, Van Houten, Hill, and Parsons (1975) examined the contributions of each of the elements of the performance feedback system used in Van Houten, Morrison, Jarvis, and MacDonald (1974). Van Houten, Hill, and Parsons continued to use informational feedback, public posting of performance, and explicit timing, but also added contingent teacher praise to the package. Elements of the package were added and subtracted in an ABCBCDC design in two fourth grade classrooms, and all of the elements were found to increase writing fluency except for praise in one of the classrooms. In addition, when the components were implemented together in a fifth grade classroom, they substantially increased students' rate of completing language arts exercises.

Finally, Van Houten (1979) extended the results of the two previous studies by looking for generalization effects; students in two classrooms were given the performance feedback package from Van Houten, Morrison, Jarvis, and MacDonald (1974) but were also asked each day to complete a second writing assignment (i.e., a generalization story) during which time the intervention was never in effect. There was also a second intervention phase in which the informational feedback element included counting all action words. Performance feedback was shown in this study to increase both fluency and action word use; moreover, these effects extended to the generalization stories.

BEHAVIOR INSTRUCTIONAL FEEDBACK INTERVENTIONS

Drabman and Lahey (1974) were interested in reducing the frequency of disruptive behaviors in a 10-year-old girl and used performance feedback in their efforts. Unlike the bulk of behavior modification studies in which the feedback is constituted by tangible reinforcers accompanied by positive praise, Drabman and Lahey asked the girl's teacher to give her a point rating (on a scale from 0 to 10) every 10 minutes, reminded by a bell ringing at that interval. At the end of each 10-minute period, the teacher reset the timer and let the student know how many points she earned. Structured classroom observation was used to obtain indices of the student's disruptiveness (e.g., number of disruptive behaviors per 20 second interval), and the feedback intervention dramatically reduced the disruptiveness. An ABAB design showed a return to problem behavior when the intervention was withdrawn and a return to good behavior when the intervention was reintroduced.

RECENT EMPIRICAL APPLICATIONS OF INSTRUCTIONAL FEEDBACK

The preponderance of research examining the effectiveness of instructional feedback interventions has been limited to educational practices incorporating instructional feedback as part of a larger package of interventions (i.e., public posting, explicit timing, varying rewards, self-scoring) that were simultaneously implemented to children in classroom settings. Although the results of these studies indicated that children's academic performance improved as a function of receiving the combined interventions, few studies have systematically examined the fundamental components of instructional feedback (i.e., precision, immediacy, frequency, schedule, valence, sources) in isolation. Furthermore, the extent to which instructional feedback interventions are appropriate for heterogeneous classrooms, where children's academic skills may vary considerably, has not been discussed. Recently, we have conducted a number of studies examining the effects of an instructional feedback intervention on children's academic achievement in writing and mathematics. The objective of these studies has been to investigate the informational component of instructional feedback in isolation. In these studies, the participating children were enrolled in rural and urban school settings, and the majority of children were functioning at an instructional (i.e., average) or frustrational (i.e., struggling) level in the targeted academic content area. We will present an overview of the basic components of the instructional feedback intervention, and then summarize the results of our work supporting the effectiveness of this intervention.

The instructional feedback intervention is comprised of two activities requiring a total of 15 to 20 minutes per session. In the first activity, students are provided with feedback regarding their writing performance from the previous writing session. The students are provided with an individualized feedback packet, which includes three instructional feedback sheets: (a) an instructional feedback sheet regarding the total number of words written from the previous session; (b) an instructional feedback sheet regarding the total number of sentences written from the previous session; and (c) an instructional feedback sheet regarding the number of correctly spelled words from the previous session. Adjacent to the feedback box is an arrow, indicating improvement (↑) or weakening (↓) of the associated skill. The research assistant reviews the individualized feedback packets as the students examine their own packets. In the second activity, the students are required to complete a written composition using a story stem (e.g., "I never dreamed that the door in my bedroom would lead to . . .). The research assistant reads the story stem aloud, the students are given one minute to think of a story based on the story stem, and then the students are given three minutes to compose the story. The intervention is implemented weekly and the students' writing fluency is also assessed weekly.

In our first study, 50 third grade children enrolled in four general education classrooms were randomly assigned to one of two conditions: (a) control and (b) instructional feedback (Eckert, Rosenthal, Benson, Mirabito, and Vance, 2005). Classrooms assigned to the instructional feedback condition received the intervention as described above. Classrooms assigned to the control condition received the same amount of time and used identical materials to complete a written composition, but did not receive the instructional feedback activities. The procedures were implemented for eight weeks and the children's writing fluency in both conditions was assessed weekly. The children's writing progress (i.e., calendar day slope estimate) was calculated for each participant on each datum for the

number of words written and the number of correctly spelled words. Analysis of the relationship between the children's writing progress was examined by conducting a series of one-way ANOVAs. The results of this study suggested that participants receiving the instructional feedback condition made significantly greater gains over time in their writing fluency, $F(1, 49) = 10.82$, $p = .002$, and spelling, $F(1, 49) = 13.87$, $p = .001$, than students who were assigned to the control condition (see Figure 1).

A second study was conducted to examine the effects of varying the amount of instructional feedback on 42 third grade children enrolled in three general education classrooms (Rosenthal and Eckert, 2005). The classrooms were randomly assigned to one of three conditions: (a) control; (b) instructional feedback once per week; and (c) instructional feedback three times per week. Sessions were conducted three times per week for 20 minutes. Children assigned to both instructional feedback conditions received the intervention as previously described and composed stories three times a week. However, children assigned to the instructional feedback once a week condition received their instructional feedback package on the last session of the week, whereas children assigned to the instructional feedback three times a week condition received instructional feedback packages each session. Children assigned to the control condition received the same amount of time and used identical materials to complete a written composition, but did not receive the instructional feedback activities. The procedures were implemented for six weeks and the children's writing fluency was assessed weekly. There were statistically significant differences in mean slopes across the three groups in writing fluency, $F(1, 41) = 3.28$, $p = .03$. Post hoc analyses indicated a significant difference between the control and instructional feedback conditions, but no statistically significant difference was found between the two instructional feedback conditions. Specifically, students receiving feedback once or three times a week on their writing performance made significantly more growth in their total written words, as compared to those students who received no feedback. Results indicated no statistically significant differences between the control and two instructional feedback conditions for the number of correctly spelled words, $F(1, 41) = 2.27$, $p = .07$ (see Figure 2).

In our third study, we examined the effectiveness of an individualized performance feedback intervention on 62 third grade children's mathematics fluency (Eckert, Rosenthal, Jiao, Ricci, Benson, Mirabito, and Vance, 2005). The children were enrolled in four general education classrooms and were randomly assigned to one of two conditions: (a) control and (b) instructional feedback. Classrooms assigned to the instructional feedback condition received the intervention as described above. Classrooms assigned to the control condition received the same amount of time and used identical materials to complete a packet of basic multiplication facts (e.g., $7 \times 9 = ?$), but did not receive the instructional feedback activities. The procedures were implemented for seven weeks and the children's computational fluency in both conditions was assessed weekly. The children's computational fluency was calculated for each participant on each datum for the number of digits correctly computed. Analysis of the relationship between the children's computational fluency progress was examined by conducting a one-way ANOVA. The results of this third study suggested that participants receiving the instructional feedback condition made significantly greater gains over time in their computational fluency, $F(1, 61) = 10.03$, $p = .002$, than students who were assigned to the control condition (see Figure 3).

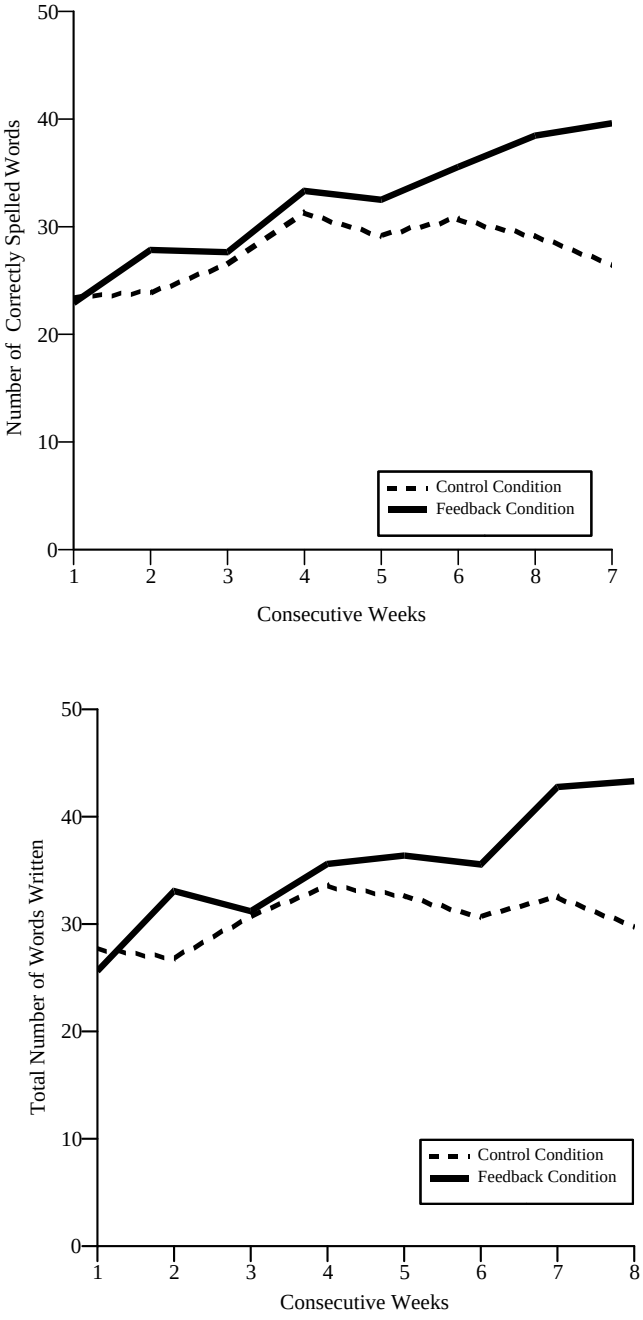

Figure 1. Results of instructional feedback on third grade children's writing fluency. Top panel: The total number of words written as a function of condition across consecutive weeks. Bottom panel: The number of correctly spelled words as a function of condition across consecutive weeks.

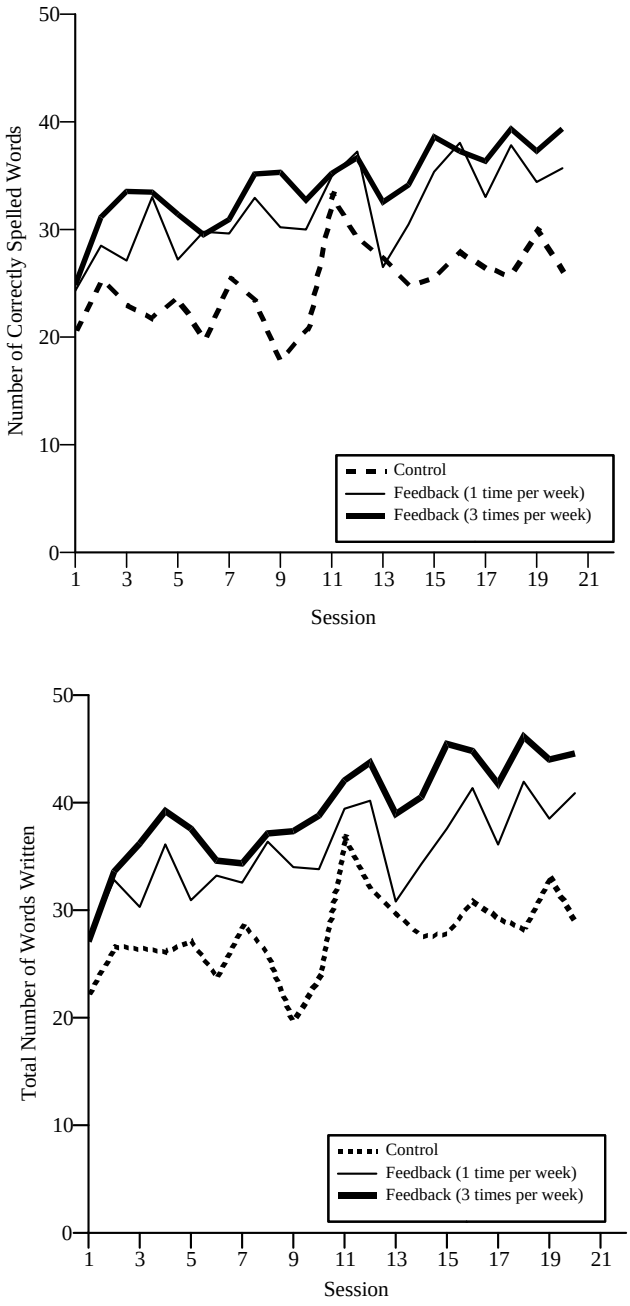

Figure 2. Results of instructional feedback frequency on third grade children's writing fluency. Top panel: The total number of words written as a function of condition across consecutive weekly sessions. Bottom panel: The number of correctly spelled words as a function of condition across consecutive weekly sessions.

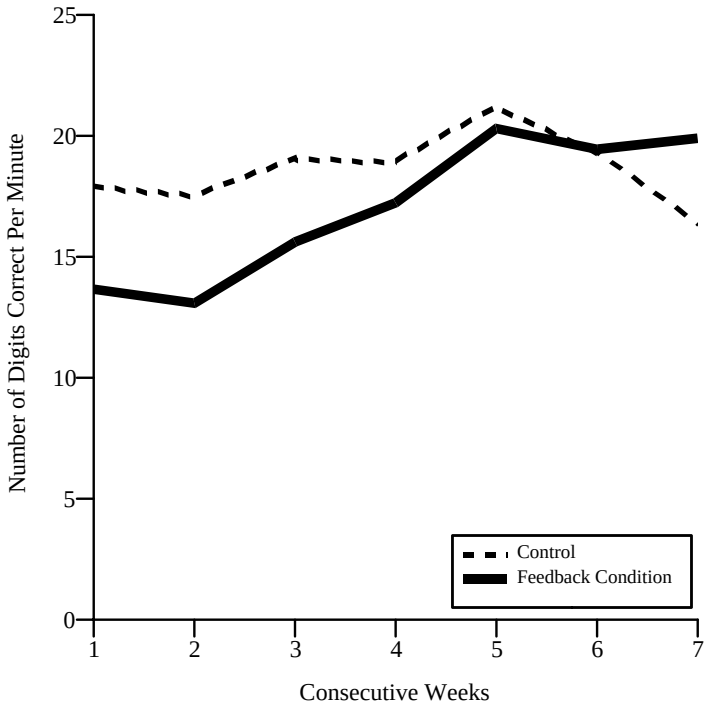

Figure 3. Results of instructional feedback on third grade children's mathematics fluency. Top panel: The total number of digits correct per minute as a function of condition across consecutive weeks.

CONCLUSION

Our review of past research on performance feedback interventions showed evidence for robust effects across subject area and age group. Our recent research is building on these findings to identify whether feedback per se (i.e., feedback construed narrowly to mean informing students privately about their performance) is sufficient to show these effects, and our preliminary findings suggest that it is. At an intuitive level, this should not be very surprising. In areas outside academics, we know that students will not learn efficiently without feedback. No football coach expects his team members to improve their performance without constant feedback that differentiates inadequate, barely satisfactory, and excellent performance. No music teacher expects that practice alone will lead to proficiency in playing a musical instrument. Perhaps it is our increasing use of achievement test results to assess teachers, schools, and school districts rather than individual students that we have neglected to recognize the importance of sharing performance information with students. In any case, a review of the literature on instructional feedback takes away any excuse for not doing so now.

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Chapter 9

LANGUAGE EVENT-RELATED POTENTIALS IN POOR READERS

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ABSTRACT

Poor Readers (PR) constitute the greater population of reading-disabled children in our country. According to Rayner and Pollatsek (1989), PR have milder reading difficulties than dyslexics, a normal IQ and their scores in standardized reading test are between one and two standard deviations below normal readers. Although scarcely studied, it is known that semantic and syntactic abilities are affected besides their deficiencies in phonological and working memory processes in both PR and dyslexics, though not merely a consequence of them.

This study aimed to find electrophysiological differences in semantic and syntactic processes between normal readers and PR during reading tasks, through the study of two language event-related potentials (ERP): N400 a component related to semantic processing and P600 related to syntactic processing.

PR showed decreased N400 amplitude to incongruent endings in compared with controls, which can be interpreted as a sign of PR's deficit in lexical integration process. This deficit probably means a more superficial lexical integration processing of PR than a more comprehensive one of the control children. Thus, reduced N400 amplitude could be the sign of a slight, incomplete or inefficient lexical searching through the internal lexicon that produces a deficient reading comprehension. This finding is different to what has been found for dyslexics or language-impaired children where larger N400 amplitude of the disabled groups has been reported. It points out that these groups of disabled children though apparently similar, really display different cognitive characteristics as revealed by ERP.

On the other hand, PR also failed to show the so-called P600 effect –that is greater P600 amplitude for ungrammatical respect to grammatical sentences- that normal readers displayed. It reveals an undifferentiated processing for syntactically correct or incorrect sentences. This could be an electrophysiological sign of PR's syntactic deficit that has been reported only for behavioral measures.
Our study provides neurobiological basis of the semantic and syntactic deficits that PR show during reading.

INTRODUCTION

This chapter attempts to provide some data about language processing during reading in poor readers studied through the Event-Related Brain Potentials (ERP) method.

The study of specific disabilities for learning to read implies interesting challenges from the point of view of the analysis of cognitive processes implied in its arising as well as designing strategies that help to improve affected skills in these children. Theoretical and methodological contributions from Cognitive Psychology, Psycholinguistics and Neuropsychology have been attempted to solve this complex problem. This chapter addresses a neurobiological approach of learning disabilities dealing with ERP investigations of semantic and syntactic processing during sentence reading in poor readers who comprise a considerable percentage of children with academic difficulties attending primary schools.

We review first some basic concepts about learning disabilities and specific disabilities for learning to read, focusing on the main characteristics of "Poor Readers". Next, we offer a brief review on ERP and its general characteristics, emphasising ERP studies of language in children. Finally, we described ERP studies of semantic and syntactic processing of sentences in poor readers that show some linguistic deficiences of these children at the physiological level.

LEARNING DISABILITIES AND SPECIFIC DISABILITIES FOR LEARNING TO READ

According to the literature, Learning Disabilities (LD) are the most common condition between developmental disorders. LD refers to "difficulties to develop specific abilities, such as writing, reading, math and language in spite of the adequate instruction and intact neurological functioning of the subject".

The definition used to clasiffy children as learning-disabled is still a controversial matter having important implications for identification, service provision and research (Beitchman and Young, 1997). The most cited and utilized definition according to Hammill (1990) is that of the National Joint Committee on Learning Disabilities, which states: "Learning disabilities is a general term that refers to a heterogenous group of disorders manifested by significant difficulties in the acquistion and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are intrinsic to the individual, presumed to be due to central nervous system dysfunction, and may occur across the life span. Problems in self-regulatory behaviors, social perception and social interaction may exist with learning disabilities, but do not by themselves constitute a learning disability" (NJLCD, 1988).

In Mexico, the General Management of Special Education -from the Public Education Ministry- accepts that about a 10% of the global population at school-age, requires its services. From them, two thirds corresponds to LD children, so it is deduced that the prevalence of LD in Mexico could be between 6 and 7% of the general school-age population (Fletcher and Kaufman, 1995).

It is considered that four of every five LD children, present a specific disability of learning to read, so specific reading disability is the most common disorder between LD. As DSM-IV-TR establishes, a person can be diagnosed as reading disabled when his/her reading level is significantly below the expected level, given his/her age, IQ and educational level (American Psychiatric Association [APA], 2000).

Nonetheless, research in the neuropsychology of reading disabilities has demonstrated heterogeneity in clinical symptoms that accompany this disorder. Following this idea, some authors have proposed different classifications of reading disorders into subtypes, and it is still debated whether exists a single reading disabled group composed by subjects with different degrees of reading difficulties or there are subgroups of children with qualitatively different characteristics (Badian, 1996; Perfetti, 1985; Rayner and Pollatsek, 1989; Siegel, 1992; Stanovich, 1988).

For instance, Rayner and Pollatsek (1989) consider the existence of three subgroups of reading-disabled children: 1) “Poor readers” (PR), (about 13% of U. S. child population) those who on the standardized reading tests score between one or two standard deviations below the norm, but have a normal IQ; 2) “dyslexic readers”, (represent 2% of child population in U.S.) those who show a discrepancy between their IQ and their performances on reading tasks; they have a normal or above normal IQ and their scores in reading tests are two or more standard deviations below the norm, and 3) “backward readers” who have low reading performance with low general intelligence.

However, other authors only distinguish between dyslexics and poor readers (Badian, 1996; Perfetti, 1985; Stanovich, 1988), or do not distinguish subgroups at all (Mann, 1998).

In this chapter, we adopt the term Reading Difficulties (RD) as a general label that includes all reading problems in children, and we will refer to dyslexics and poor readers as defined by the above-reviewed criterion of Rayner and Pollatsek (1989).

In spite of the high incidence of poor readers in child population, most studies of RD children have focused on dyslexics, that have been studied from several viewpoints (neuroanatomical, neuropsychological, genetical and electrophysiological), while the majority of studies done in PR come from neuropsychological examinations.

COGNITIVE DEFICITS IN RD

As mentioned above, several investigations concluded that RD children form a heterogeneous group, which hold deficiencies in various stages of information processing by the central nervous system. For this reason, a precise identification, diagnosis and intervention on this disorder require methods that specifically assess those processes affected. Deficits in language processing, working memory or attention (as comorbid with learning disabilities) have been proposed as the source of reading failures exhibited by RD children (Mann, 1998; Swanson and Sáez, 2003; Conte, 1998).

Nonetheless, current evidence indicates that deficits of phonological processing skills are the core underlying this disorder (Beitchman and Young, 1997; Mann, 1998; Stanovich, 1988).

It is important to mention some differences between dyslexics and PR that may point out to different causes that lead to each subtype of the disorder. In this way, we have that unlike dyslexics, PR: a) do not have a history of language impairment prior to their reading deficits (Tallal, Miller and Fich, 1993; Anderson, Brown and Tallal, 1993); b) tend to ameliorate reading deficits with age (Kinsbourne, Rufo, Gamzu, Palmer, Berliner, 1991; Anderson et al., 1993; Rutter, 1978); c) do not show the brain abnormalities that have been advanced for dyslexics (Galaburda, Sherman, Rosen, Aboitiz and Geschwind, 1985; Hynd, Semrud-Clikeman, Lyytinen, 1991; Hynd et al., 1995; Habib, 2000) and d) show slower EEG activity than normal subjects (Harmony, et al., 1995). There is abundant evidence of phonological deficits of children with reading difficulties (either dyslexics or PR) (Beitchman and Young, 1997; Stanovich, 1988; Wagner and Torgesen, 1987) and their impairments in working memory have also been pointed out (Swanson, Cocney, O'Shaughnessy, 1998; Swanson and Sachse, 2001). In dyslexics a specific "temporal processing impairment" may underlie some of the perceptual, motor and cognitive abnormalities found in these children (Habib, 2000; Tallal et al., 1993). Despite the above mentioned findings, nowadays there is no an explicit hypothesis about biological causes of reading deficiencies of PR.

Some evidence allows us to conclude that although dyslexics and poor readers share affected cognitive processes such as phonological processing and working memory deficits, there are some differences between them. For instance, Stanovich (1988) suggests that phonological problems of the PR are milder than those of dyslexic children.

Given the variability of symptoms presented in RD, it is unlikely that all of them could be explained solely by phonological deficiences. Among others, it has been proposed that deficits in their semantic and syntactic skills along with a weak working memory capacity, could explain low scores obtained by PR in these kinds of tasks.

Thus, some authors provided evidence of a variety of semantic failures that include worse performances in object naming and pseudowords identification tasks (Vellutino, Scanlon, and Tanzman, 1988; Vellutino, Scanlon and Spearing, 1995; Champion, 1997; Gillon and Dodd, 1994; Stelmack, Saxe, Noldy-Cullum and Campbell, 1988). Some studies have reported differences favoring normal readers in semantic memory as well as semantic learning tasks using visual symbols and paired associates (Vellutino and Scanlon, 1985; Vellutino et al., 1995; Waterman and Lewandowski, 1993).

Syntactic failures of PR have been demonstrated in ordering of sentences and identification of sentences with syntactic violations (Byrne, 1981; Siegeel and Ryan, 1988).

For Spanish-speaking children, semantic-syntactic deficiencies in language processing have also been demonstrated (Cuetos,1998) as well as in Mexican children attending public schools, who performed neuropsychological batteries including those kind of tasks as ordering words into syntactically correct sentences, detection of grammatical errors in sentences, construction of sentences and comprehension of written texts (Silva et al., 1995; Yáñez et al., 2002).

Finally, we can say that Poor Readers (PR) constitute the greater population of reading-disabled children in our country. According to Rayner and Pollatsek (1989), PR have milder reading difficulties than dyslexics, a normal IQ and their scores in standardized reading test are between one and two standard deviations below normal readers. They otherwise comprise

a very heterogeneous population and deficiencies in several mechanisms have been proposed to explain their reading deficiencies. Among these mechanisms are: deficiencies in phonological skills, working memory low capacity, and deficits in syntactic/semantic processing, to mention a few.

EVENT-RELATED BRAIN POTENTIALS (ERP)

One of the most useful techniques for the study of physiological bases of cognitive processes in humans is the ERP method. ERP allows the study of cognitive processing with a high degree of temporal resolution (in the order of milliseconds). "ERP can be defined as patterned voltage changes on the ongoing electroencephalogram that are time locked to sensory, motor, or cognitive events. ERP arises from synchronous activities of neuronal populations engaged in information processing (Hillyard and Picton, 1987)".

These voltage changes are generally smaller in amplitude than the continuous background electrical activity, called the electroencephalogram (EEG). In order to extract the event-related activity from the ongoing electroencephalogram, the most common procedure is to average several EEG responses that are time-locked to the stimulus of interest.

ERPs consist of a series of positive and negative voltage peaks or components that appear with specific time delays after the appearance of stimulus that elicited them. The height of the voltage peak is called the amplitude of the component (measured in microvolts) and the time delay is named its latency (measured in miliseconds). Topographical distribution –those regions of the scalp where the peak is recorded with maximum amplitude- is another parameter usually studied.

ERP components have been named according to their positivity or negativity and their latency. In this way, P200 –for instance- means a positive component ocurring approximately 200 milliseconds after the onset of the stimulus, or N400 is a negative component appearing about 400 milliseconds after the beginning of the stimulus event.

The early ERP components that occur with latencies below 60-80 ms, are determined primarily by the physical characteristics of the eliciting stimulus, and are relatively insensitive to changes in the psychological state of the subject. In the literature, these responses have been named exogenous.

In contrast, many of the later ERP components are highly sensitive to changes in the psychological state of the subject, the meaning of the stimulus, and/or the information-processing demanded by the task. These components have been named endogenous and they are useful for investigating the physiological bases of human perception and cognition (Hillyard and Picton 1987) and have helped us to understand the differences between normal and abnormal information processing.

P200, N200, P300 and N400 are some of the best-studied endogenous components. They have been related to different phases of information processing. These components may show changes in amplitude and/or latency depending on psychological states and experimental conditions. The physiological mechanism underlying in low amplitudes may consists of less brain structures involved in the task or different timing in the synchronization of neural generators. A delayed latency of these components may reflect long times for processing

information related to stimulus. When, otherwise, high amplitudes and short latencies of ERP are observed, maybe the opposite physiological mechanism occurs.

ERP IN THE STUDY OF LANGUAGE

The use of ERP technique for the study of language is based upon the suposition that different cognitive processes are mediated by different patterns of cerebral activity. This principle enables to study separately the levels of linguistic representation, i.e. phonological, semantical and syntactical, in order to evidence distinct ERP patterns. Because of the great temporal resolution of ERP, one may know the exact succession of a great quantity of brain electrical responses elicited by the presentation of a stimulus, and make inferences about their corresponding cognitive event.

A fruitful approach in the study of language with ERP has been the recording of brain activity related to the detection and processing of a variety of "linguistic errors" such as semantic or syntactic anomalies. Two ERP components associated with these anomalies are N400 and P600, respectively.

N400

N400 is an ERP component related with specific aspects of language processing (Kutas and Van Petten, 1988; Osterhout and Holcomb, 1995). The N400 has a negative polarity and it peaks around 400 ms after critical stimulus onset.

It is elicited by any meaningful word presented either in isolation, in pairs of words (i.e. priming paradigms) or in sentences (Brown, Hagoort and Kutas, 2000). It is widely distributed over the scalp, with a tendency toward greater amplitudes over central and posterior electrode sites.

It was originally described as a cerebral response to semantic incongruencies found in read sentences by Kutas and Hillyard (1980). They described that N400 was elicited by the last word of both congruent and incongruent sentences nonetheless it was of greater amplitude for the incongruent ones (called N400 effect).

The N400 can be manipulated by a number of variables known to affect the extraction of meaning in a written or spoken sentence, such as word frequency, cloze probability and strength of semantic priming. The N400 amplitude is an inverse function of the amount of semantic priming that a word has received from a preceding context.

Neville, Coffey, Holcomb and Tallal (1993) confirmed that N400 amplitude is negatively correlated with both word frequency and semantic context (Holcomb, 1988; Kutas and Hillyard, 1984; Neville, Pratarelli and Forster, 1989; Rugg and Doyle, 1992), and therefore it is reasonable to assume that it indexes processes involved in the integration of a word into the context (Holcomb and Neville, 1990; Rugg and Doyle, 1992).

It has been shown that N400 varies systematically with the processing of semantic information (Kutas and Federmeier, 2000). Although it is especially large to semantic information, the N400 is not simply an index of anomaly, but rather a part of the brain's normal response to words (Brown et al., 2000). The prevalent view of the functional

interpretation of N400, or more precisely of N400 effect is that it reflects 'lexical integration' processes. Thus, after a word has been activated in the mental lexicon, its meaning has to be integrated into a higher-level conceptual representation of the context within it occurs. This meaning-integration process is manifested in the N400 effect. The more difficult the integration process is, the larger the amplitude of N400 (Brown and Hagoort, 1993, 1999; Kutas and King, 1995; Osterhout and Holcomb, 1992).

P600 AND LAN

In contrast to semantic processing, an ERP component related to syntactic processing is still not found, at least one being universally accepted (Gunter, Stowe and Mulder, 1997). ERP investigations of processing of syntactic violations in adults have reported two components: 1) The Left Anterior Negativity (LAN) which is an early component starting between 250 and 300 ms post-stimulus, with a topographical distribution in left anterior scalp region. It has been related to processing of the syntactic category of the word to be read. Other researchers propose that LAN is a reflection of working memory processes during language comprehension, related to the activity of holding a word in memory until it can be assigned its grammatical role in a sentence (Brown et al., 2000; Kutas and King, 1995). However, its exact functional nature is still under study. 2) The P600, is defined as a late bilateral positivity with onset at 500 ms after the presentation of the syntactically anomalous word, persisting for some hundred of milliseconds, with a centroparietal distribution. It is also named Syntactic Positive Shift (SPS) (Neville, Nicol, Barss, Foster and Garrett, 1991; Osterhout and Holcomb, 1992; Hagoort, Brown and Groothusen, 1993; Osterhout, McLaughlin and Bersick, 1997; Canseco-González, 2000).

P600 is elicited by a variety of syntactic violations -such as phrase structure, verb subcategorization, subject-verb number agreement, reflexive-antecedent gender agreement or reflexive-antecedent number agreement- that involve different aspects of grammar. The fact that each one of the previous violations yields P600 accounts for the relationship of this component with syntactic processing. At the same time the heterogeneity of syntactic phenomena associated with P600 raises questions about exactly what the component is reflecting about language process (Brown et al., 2000).

At present, a clear functional interpretation of P600 is not yet avalaible. Some investigators claim that it is a member of the P300 family and that it is not necessarily produced by linguistic events (Coulson, King and Kutas, 1998). However, Osterhout, McKinnon, Bersick and Corey (1996) found that P600 is independent of P300 effect.

Other authors have suggested that P600 reflects specifically the gramatical processing related to the reanalysis that occurs when the parser fails to complete syntactic analysis whenever some ambiguity or syntactic violation is found; in this manner, this reanalysis rescue the meaning of the sentence (Frederici and Mecklinger, 1996; Hagoort et al., 1993; Münte, Heinze, Matzke, Wieringa and Johannes, 1998).

It can be concluded with Frederici, Mecklinger, Spencer, Steinhauer and Donchin (2001) that P600 is a component that reflects a mixture of subprocesses including diagnosis, syntactic reanalysis, revision and semantic integration. Another interpretation points out that P600 relates to a late syntactic analysis in which intervenes simultaneously a semantic

analysis (Gunter et al., 1997). Finally, it has also been suggested that this component could reflect a reinterpretation process through which the subject tries to find the meaning of a sentence after having noted a grammatical error (Canseco-González, 2000).

Although theoretical explanations about reading process point out to a close relationship between syntactic and semantic analysis, on electrophysiological grounds it is clear that ERP components related to both processes display different characteristics. For this reason it is considered that syntactic and semantic processes have different neural bases (Brown et al., 2000).

EARLY VISUAL ERP COMPONENTS: P150, N150, P200

Several studies pointed out the importance of evaluating early components of ERP, since it had been shown that they reflect physiological events relevant to the study of information processing, such as: 1) early attentional priming related to linguistic stimuli: N150 (Neville, Kutas, Chesney, Schmidt, 1986), 2) early visual processing: P150 (Mangun, Hillyard, Luck, 1993; Neville et al., 1993; Taylor, 2002) or 3) changes related to attentional demands of a task: P200 (Johnson, 1989; Licht, Bakker, Kok, Bouma, 1988).

Longitudinal studies of children have shown that the amplitudes and latencies of these components tend to decrease with age (Johnson, 1989; Holcomb, Coffey and Neville, 1992; Taylor and Khan 2000). In a group of language-impaired (LI) children, Neville et al. (1993) found decreased amplitude of P150 and P350 as compared to normal subjects that was interpreted as a reflection of early sensory processing deficits in the LI children. Stelmack et al. (1988) reported increased P200 amplitude in PR during reading and recall of isolated words, as well as Bernal et al. (2000), who in an auditory oddball task found larger P200 amplitude to both frequent and infrequent stimuli in PR in comparison to normal subjects. Stelmack et al. discussed their findings as differences at an early sensory stage of stimulus processing between groups, meanwhile Bernal and colleagues suggested that PR allocated attentional resources in earlier stages of information processing (i.e,. P200). The later assumed that normal subjects displayed more attentional resources in stages corresponding to the evaluation of stimuli (i.e., P300). Furthermore, Silva-Pereyra et al. (2003) reported larger P200 amplitudes in PR during a word categorization task, and claimed that PR allocated more attentional resources than controls during word processing. Finally, Robichon, Besson and Habib (2002) found no differences in the N1-P2 (N150-P200) sensory component between dyslexic and control adults in a sentence reading task performed at fast or slow rates of presentation.

LANGUAGE ERP STUDIES IN CHILDREN

The study of the electrophysiological correlates of the language in the brain of children through the use of ERP has been focused to studies investigating language development primarily in the area of speech perception and phonological development in early childhood, both are important during the development of language abilities. This kind of studies is not

the matter of this chapter and are reviewed elsewhere (Molfese and Molfese, 2000; Cheour, Leppanen and Kraus, 2000; Leppanen and Lyytineen, 1997).

When studying the neural basis of language, one important problem comes from the selection of the task. The number and type of language functions considered has increased, as the methods for assessing language functions, resulting in the breakdown of language into subcomponents including phonology, phonetics, syntax, semantics, and pragmatics. However, even simple tasks, hypothesized to index selectively particular aspect of language processing, often do not tap only one component, but encompass a complex chain of processing. This renders the linguistic process we want to characterize and the various activities related to the task difficult to break apart. Moreover, it has also been noted that constrained tasks, such as a purely phonetic task, are often highly unnatural and may encourage subjects to rely on strategies that are only remotely related to those playing during natural language processing. For these reasons, a number of authors have argued for the use of tasks that are cognitively natural for the skill studied (Demonet, Wise, Frackowiak, 1993). This is the case for the use of sentences rather than isolated words, commonly used in experiments of this area. While both words and sentences engage lexical analysis, aspects of syntactic and semantic analysis are unique to sentence comprehension (Bavelier et al., 1997). Consequently, we seek to review relevant studies about the neurological bases of semantic and syntactic processing of language comprehension in normal and reading disabled children.

Because ERP can be used for chronometric analysis of cognitive processing, yielding information not avalaible from behavioral measures, they are well suited for investigation of multiple levels of cognitive processing for reading. A lot of investigations deal with behavioral research on reading, physiological studies using ERP are comparatively scarce. This is particularly true for children, where the usual stimulation paradigms involved in lexical decision tasks may be seen as a less natural way than reading sentences. In the next paragraphs, we review ERP studies related to semantic and processing of language in normal and reading disabled readers.

SEMANTIC PROCESSING: N400 IN CHILDREN

A few recent studies have examined developmental changes in language-sensitive ERPs through childhood. Holcomb et al. (1992) studied subjects aged 5-26 years old, when they listened to and read (7-26 years) sentences that ended either with a highly expected or a semantically innapropiate word. ERPs to final words of the sentence displayed effects of contextual priming in both modalities in all age groups. They found that N400 displayed a large decrease in amplitude and latency with age, and the authors concluded that there were significant reductions in the semantic priming effects with age, which reflects that as children acquire better reading skills, they rely less on semantic context for language comprehension.

Neville et al. (1993) thoroughly studied a group of Language Impaired (LI) children, who were also reading disabled, using perceptual as well as linguistic tasks. They found that specific aspects of sensory and language processing were abnormal in the LI group as a whole, while other aspects were aberrant only in subsets of the language-impaired sample. This fact made the sample heterogeneous, as usual in this type of disorders. In sensory processes, auditory N100 (N140) was abnormal in a subset of children having worse

performance in an auditory temporal discrimination task, while early visual components P150 and P350 – which have been related to early visual processing - were reduced in amplitude in the whole group. For linguistic tasks, the authors employed a sentence-reading paradigm, in which the LI subjects who could read well enough, showed a tendency to have greater N400 amplitude than control subjects. This result was interpreted as LI children required more effort in integrating words into contexts determined by sentences, so they relied more on context for word recognition than control subjects did.

Rodríguez et al. (2005) studied a group of PR children (10-12 years old) in a sentence-reading paradigm, analyzing the early visual ERP components and the N400 component. They concluded that for PR, reading demands more effort and attention than for normal readers as revealed by greater amplitudes of the early components in PR respect to normal children. Regarding the N400, PR showed smaller N400 amplitude for congruent and incongruent endings and prolonged latency of the N400 effect, reflecting an inefficient and slower lexical integration process. The interpretation given to these findings was that for PR, reading is not an automatized process both during early analysis of linguistic information and during lexical integration.

With some different approach, Stemack et al. (1988) compared ERP responses of normal readers with reading disabled children to tasks that involved both encoding and retrieval of words. They found increased P200 amplitudes and decreased N400 amplitudes in reading-disabled compared to controls, and interpreted the first finding as a sign of greater effort in early processing of word reading, and diminished N400 amplitude as a failure of semantic evaluation or memory search attributed to that component. Moreover, in a lexical decision task with word-pairs, “reading/spelling deficient children” exhibited reduced N400 amplitude and absent N400 hemispheric asymmetry evident for normal controls (Stelmack and Miles, 1990), whereas reading-disabled children showed priming deficiences, which probably indicate impaired auditory-verbal processes (Miles and Stelmack, 1994).

Silva-Pereyra et al. (2003) attempted to evaluate how PR could access semantic information independently of stimulus kind. They used a figure and a word categorization task. For word categorization task (a decision between animal and non-animal stimuli), PR presented larger P200 amplitudes and smaller amplitudes and longer P300 latencies than controls. Nonetheless, there were no between-groups differences in the N400 component. They suggested that PR’s low performance in semantic tasks may be due to early deficiences in the processing of words, which are reflected in larger amplitude of P200 component, and not because of a semantic deficit per se, reflected in the PR’s normal N400 response.

To summarize, the studies of N400 in reading-disabled (RD) children have shown basically two opposite results: 1) A larger N400 amplitude in controls with respect to RD, during sentence-reading (Rodríguez et al., 2005) or in tasks that have comprised silent reading of words and the subsequent word recognition memory task, or a picture priming task, where words were preceded by a picture that had or had not the same denotative meaning (Stelmack et al., 1988; Stelmack and Miles, 1990). The authors interpreted this finding as a failure of the RD to engage long-term semantic memory. Recently, it has been reported that the word-naming deficit of RD is a specific linguistic deficiency reflected in a reduced N400 amplitude (Greenham, Stelmack, van der Vlugt, 2003), and 2) A larger N400 amplitude in LI children with respect to controls during reading of congruent and incongruent sentences (Neville et al., 1993). This fact was interpreted as “compensatory increases in the

effort required to integrate words into context". Similar results were found by Robichon et al. (2002) in adult dyslexics, while reading sentences.

These apparently contradictory findings may be due to different cognitive characteristics of the samples, i.e., while LI and dyslexics may show severe reading difficulties, other clinical subgroups as those studied by Stelmack et al. could have less severe symptoms.

SYNTACTIC PROCESSING

Neville et al. (1993) analyzed ERP for function words and content words in normal and language-impaired children. For normals (8-10 years old), ERP corresponding to function words displayed a hemispheric asymmetry toward the left. A similar pattern was seen for LI children with high syntactic ability, but a hemispheric reversal was observed for LI children with low syntactic ability. No differences were reported for the content words. These findings point out for an early hemispheric especialization for function words clearly related with syntactic processing of language.

A recent developmental study by Hahne, Eckstein and Friederici (2004) reported ERP responses of normal children (6 to 13 years old) that listened to passive sentences that were correct or semantically or syntactically anomalous. For the later type of sentences, the authors used a phrase structure violation, and described a syntactic negativity (named "early left anterior negativity") and a late positivity (P600) for children between 7 and 13 years. The six-year-olds did not demonstrate the early left anterior effect, but a late, reduced P600 pattern for the syntactic violation condition. Latencies of these components decreased with age and no topographical changes with age were reported.

In Mexican Spanish-speaking children (8-11 years old), Avecilla-Ramírez, Silva-Pereyra, Harmony, and Sánchez (2004) investigated the effects of the working memory load capacity in PR and normal children groups. The ERP experiment comprises two tasks, one of acceptability judgment where children had to read and judged as correct or incorrect sentences with and without syntactic and semantic anomalies. The second (named working memory task) included reading a series of sentences, judging their correctness and reteining the last word of each sentence in memory in order to recall it two or three sentences later. For syntactic violations, a P600 was described in normal children in the acceptability judgment task. During the working memory task, normal readers showed a decrease of P600 effect. In contrast, no significant P600 effect during either the acceptability judgment task or the working memory task were found in their group of PR. The authors suggest that working memory in PR may be taxed to the maximum even when the subjects just have to read the sentences. It points out that reading and acceptability judgment task are high memory demanding in ERP paradigms, and this demand is especially critical for PR, considered to have a low capacity working memory.

CURRENT STUDY

The general objective of this research was the electrophysiological and neuropsychological analysis of the cognitive characteristics of school-aged Mexican PR of

urban zones and middle socio-economic level. Specifically in this study, we aimed to shed light on PR´s deficits associated with their semantic and syntactic processing during reading by means of two experiments.

EXPERIMENT 1: SEMANTIC PROCESSING

In the first experiment of Rodríguez et al. (2002), we studied ERP components during reading of sentences in a sample of Spanish-speaking PR. We explored the mechanisms of integration of words into sentence contexts, using N400, as an index of contextual processing. Mechanisms of early visual processing (P150), attentional priming to linguistic stimuli (N150) and general attention processing in a demanding task (P200) were also explored.

As the physiological mechanisms involved in reading deficits of PR has not been yet widely explored, some outcomes can occur: a) We may suppose that PR and controls would display the same characteristics of the early sensory components, with the probable exception of P200 that might show higher amplitudes for PR respect to controls, as an index of higher attentional demand during reading in this group of disabled children, b) PR would probably display larger N400 amplitude or latency than controls, thus reflecting greater effort or slower speed in the process of integrating words into context. Alternatively, as PR show milder reading difficulties than dyslexics, PR may show reduced N400 amplitudes respect to controls as a sign of a deficit in lexical integration process.

METHODS

Subjects

A group of 18 Spanish-speaking male children, aged 9 to 12 years participated in this experiment.

The group of poor readers (n= 9) were 9 –12 years old ($\bar{X}$ = 10.33 years old), had a history of academic failure. All of the children in this group were right-handed; no one had a familiar history of left-handedness. All PR subjects had normal intelligence with a total IQ (WISC-R) between 85 and 101: $\bar{X}$ total IQ = 91.7 ± 6.05. They have no history of language impairment, and their pediatric and neurological examinations were normal.

The controls (n=9) were between 9 and 12 years old ($\bar{X}$ = 10.22 years old), had no history of academic failure. All were right-handed. Controls had a total IQ (WISC-R) score between 90 and 116: $\bar{X}$ total IQ=103.9 ± 9.6. All of them had normal pediatric and neurological examinations.

The two groups were classified according to the scores obtained in a neuropsychological and a reading battery in Spanish:

- "Neuropsychological Battery of Reading Disabilities" (NBRD) (Yáñez, et al. 2002). This battery was designed for Mexican school-aged children (7 –12 years old) and evaluates several skills related with learning of reading such as:

phonological processing, attention, receptive and expressive vocabulary, comprehension, reading, grammar, writing, arithmetic, perception and memory, and

- "The Reading-Writing Analysis Test " (RWAT) (Toro and Cervera, 1990). The later assesses speed of reading, number of correct responses in the reading of letters, syllables and words and reading comprehension. The total score in this test provides the reading level of the child.

The scores obtained by PR were one level below their corresponding scholar grade in the RWAT and between one and two standard deviations below normal's scores in the NBRD, so they can be considered PR according to the operational definition given above.

The specific NRBD's tests that were considered to classify the groups were: Accuracy and speed in word reading, comprehension in written texts and oral commands, accuracy in grammatical tasks, accuracy and speed in dictation of words and paragraphs and accuracy and speed in rapid automatized naming.The two groups of children did not differ in chronological age ($p<0.87$), but they did so, in the total IQ: $F(1,16)=10.24$, $p<.005$. All the parents of the participants gave informed consent.

Stimuli

A total of 100 sentences 4-8 words long, were presented word by word on a computer monitor, with white colored letters on a black background. The words subtended a visual angle between 0.71 and 1.43 degrees. At the beginning of each sentence a fixation signal ("XXXXXX") was presented to indicate that the child was starting to read the sentence. Words were presented for a duration of one second with an interstimulus interval of 500 ms, so the stimulus onset asynchrony (SOA) was 1.5 seconds. These durations were chosen after probing with a different sample of children that were able to read the sentences correctly with this speed of presentation.

The sentences were simple in form and content, and used well-known words according to a lexicographic dictionary, developed in Mexico by Ávila (1986, 1993). Further, the sentences had a cloze probability[10] for the children (fourth to sixth grades) greater than 0.8 (n=40); that is, more than 80% of the children tested had to fill in the appropriate best-completion final word, when giving the stem sentence ending in a blank (Holcomb et al., 1992). This was accomplished in a sample of 120 children (from fouth to sixth grades of primary school) from the same community school where the controls and PR came from.

A 50 percent of randomly chosen sentences ended in semantically anomalous, but syntactically correct word. In all cases the last word was a noun.

Procedure

Five to seven sentences were presented to the children for practice before the recording. Subjects were instructed to read silently in order to decide whether the sentence had sense or

[10] A word´s cloze probability is defined in terms of the percentage of subjects using that word to complete a particular sentence (Kutas and Van Petten, 1988. pg. 160)

not and to press a different mouse button in each case. Percentage of correct sentences and reaction times were evaluated. Only correctly answered sentences were considered for analysis.

ERP Recording

Referential EEG recordings (0.5-30 Hz bandpass) time-locked to the last word were obtained from 10-20 International System with electrode sites at Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz, with linked earlobes as reference, using Ag/AgCl electrodes. The electro-oculogram (EOG) was recorded with bipolar electrodes placed at the outer cantus and the supraorbital ridge of the left eye. Neuroscan equipment was used.

The electrode impedance was always below 10 k . The sampling interval was 5 ms over a time epoch of 1280 ms, with a pre-stimulus baseline interval of 100 ms. EEG segments were visually edited to discard any artifact or EEG activity exceeded ± 50 μV.

Data Analysis

Behavioral data were analyzed by ANOVA

For the electrophysiological data, we analyzed the amplitudes of the early components (P150, N150 and P200) and N400. For the early components, mean amplitudes in the following latency windows (corrected to the pre-stimulus baseline) were measured: P150 was evaluated as the greatest positivity between 115-135 ms only in occipital and parietal regions. N150 was the greatest negativity between 190-210 ms in frontal and central regions (i.e. F3, Fz, F4, C3, Cz and C4). P200 was defined as the greatest positivity between 210-225 ms in frontal and central regions.

For the evaluation of the N400 component, the mean amplitude values (relative to the average pre-stimulus baseline) of the negativity to the congruent and incongruent words were calculated in the interval 350-450 ms.

The effect of congruity was assessed by a 3-factor ANOVA with Congruity, and antero-posterior (with 3 levels): Frontal (F3, Fz, F4), Central (C3, Cz, C4) and Parietal (P3, Pz, P4) and coronal (with 3 levels): Left lateral (F3, C3, P3), Midline (Fz, Cz, Pz) and Right lateral (F4, C4, P4) electrode placements as factors.

The effect of group was assessed by a 3-factor ANCOVA (total IQ as covariable) with Group, and Antero-posterior and Coronal electrode placements as factors.

RESULTS

Behavioral Results

The PR group made significantly more errors identifying correctly both congruent and incongruent sentences, as revealed by percentages of correct responses: (Congruents: NR=

86.7% vs PR= 78.0% (F 1,16= 6.96 p<.01); Incongruents: NR= 90.3% vs PR= 84.8% (F 1,16= 3.65 p<.07). Furthermore, PR were significantly slower than controls in their responses for identifiying each type of sentence as shown in reaction times (RT): RT for Congruent sentences in NR= 567 ms vs PR= 723 ms (F1,16= 4.62 p<.04; RT for incongruent sentences in NR= 525 ms vs PR = 694 ms (F 1,16= 4.00 p<.06).

ERP Results

Figures 1 and 2 illustrate the ERP for the congruent and incongruent sentences in each group respectively, at 9 electrode sites. For the anterior regions, N150 was observed, (an early negativity, which peaked between 100 and 180 ms) followed by a robust positive-going wave that peaked between 200 and 300 ms, the P200. N150 and P200 form the so-called N1-P2 complex that usually appears while reading words. In posterior regions, the morphology of the ERP is different from that of the anterior ones (see Figure 1). In the first place, P150 was observed, that is a large positivity peaking between 100 and 180 ms, followed by a broad negativity. A positivity also can be observed, which peaked between 250 and 360 ms, termed occipital P250. Finally, at all electrode sites, P200 and P250 were followed by a negative component which peaked between 350 and 450 ms, the N400.

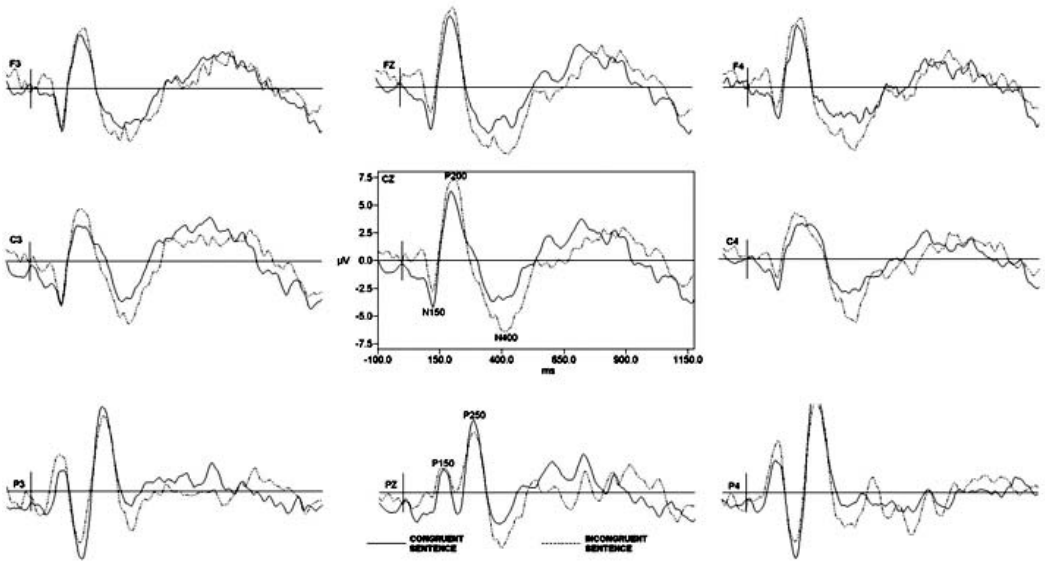

Figure 1. Grand average ERP to congruent and incongruent sentences in the control (n=9) group in 9 electrode sites. Early components: P150, N150, P250 and P200 and N400 are marked. The N400 effect (larger N400 amplitudes for incongruent than for congruent sentences) can be observed.

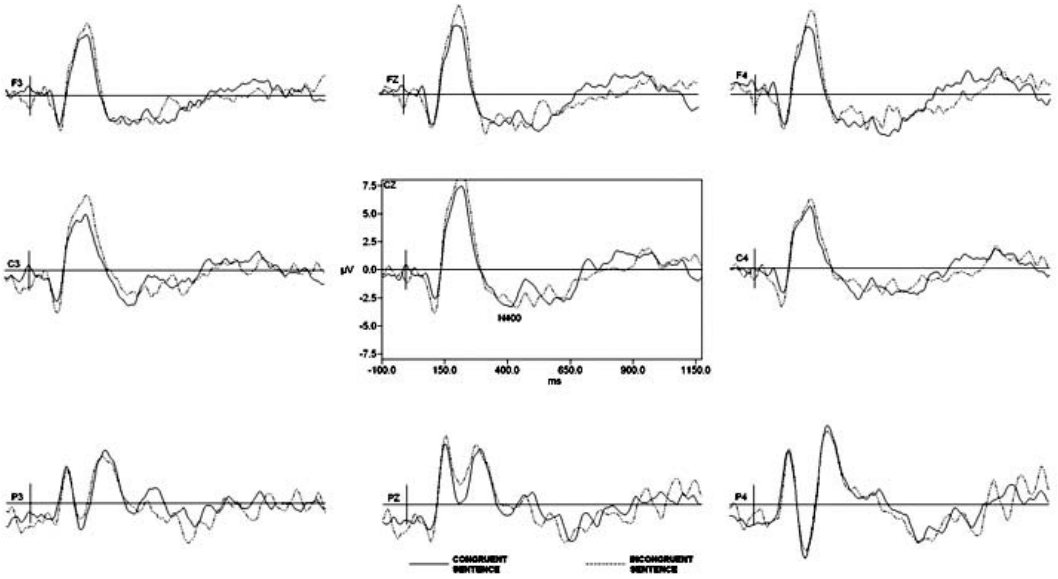

Figure 2. Grand average ERP to congruent and incongruent sentences in the poor readers (n=9) in 9 electrode sites. No clear N400 effect can be observed.

Early Components

Congruity Effect

No differences by congruity were found in amplitudes or latencies of the early components in any of the groups.

Group Effect

In this experiment it was only observed a greater amplitude of P200 component in the group of PR as compared to the controls. This effect was noteworthy at fronto-central derivations as shown in figure 3. Larger P200 amplitude of the PR group may be related to a greater effort of attention while decoding words in these children compared to normal readers.

No between-groups differences were found in P150 nor N150.

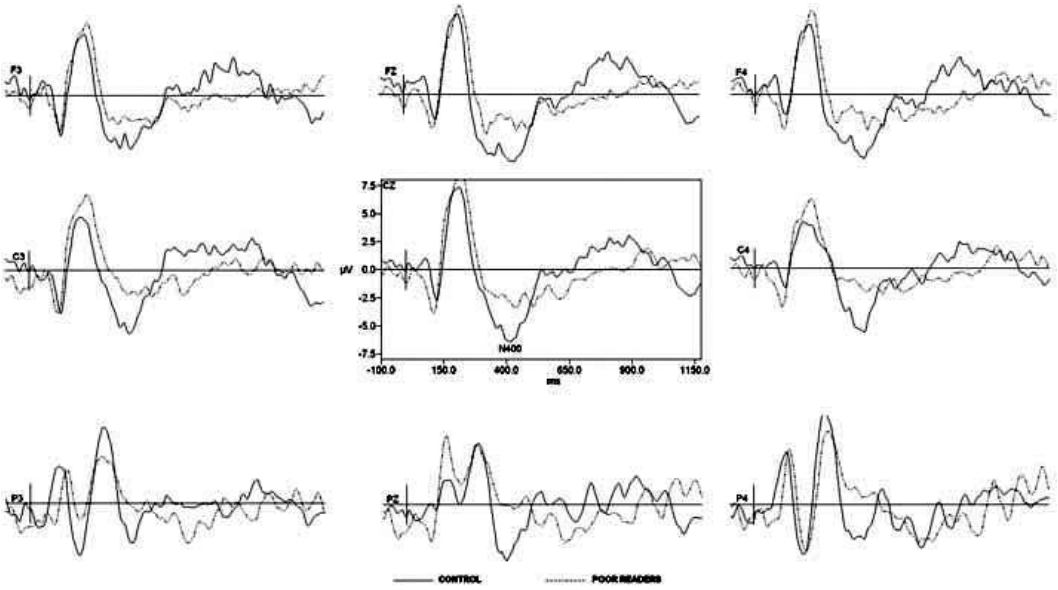

Figure 3. Grand average ERP to incongruent sentences in the control (solid line) and the PR (dashed line) groups. Larger amplitudes of the N400 component for control than for poor readers can be observed at all electrode sites, as well as larger P200 amplitudes for poor readers respect to control subjects.

N400 Component

Congruity Effect

Clear differences in ERP responses to congruent and incongruent endings were obtained in the control group, yielding to the well known N400 effect, that is greater negativity for incongruent than to congruent sentences (see figure 1).

As can be observed in figure 1, N400 effect is widespread in every lead illustrated, although it had some greater amplitude at central and parietal leads and at right larger than left derivations.

For the PR group, we did not find the N400 effect, since the negative response was similar for both types of sentences (see figure 2).

Group Effect

The control group showed significantly larger N400 amplitude than PR group for incongruent sentences. Group main effect: $F(1,15) = 4.58$ $p<.04$ (see figure 3) This greater N400 amplitude of the controls can be observed in every lead illustrated in figure 3 (i.e. central, parietal and frontal leads).

Furthermore, a topographical ANOVA of the N400 effect was done using the scaled values (McCarthy and Wood, 1985) of the N400 effect obtained by subtraction of the response of congruent sentences to that of the incongruent ones. Between-group differences showed that scaled N400 effect was larger for controls respect to PR in central, parietal and frontal leads, except for F3 derivation. This implies that N400 effect was disseminated in all the analyzed scalp regions without an evident lateralization effect, and that in every region, N400 effect was larger for controls as compared to PR group (figure 3).

EXPERIMENT 2: SYNTACTIC PROCESSING

The objective of this experiment carried out by Prieto et al. (2002) was the characterization of ERP responses during reading of sentences containing syntactic violations, in normal Spanish-speaking children along with the exploration of possible differences between normal and PR children. The paradigm included only the syntactic violation of subject-verb agreement which is easily understandable for children (Hagoort et al., 1993; Osterhout and Mobley, 1995).

We explored the mechanisms of syntactic-semantic reanalysis used when syntactic violation is found in a sentence in PR and normal children, using the P600 component. Mechanisms of early visual processing (P150), attentional priming to linguistic stimuli (N150) and general attention processing in a demanding task (P200) were also explored. As Left anterior negativity (LAN) has not been consistently reported in several studies of ERP responses to sentences with syntactic violations, we decided not to analyze it.

METHODS

Subjects

Subjects were eleven male children in each group (Normal Readers=NR and Poor Readers=PR) aged between 8 and 13 ($\overline{X}$ NR=10.18 and $\overline{X}$ PR=10.45 years old). The children participating in experiment 2 were different from those of experiment 1. Both groups of children had normal IQ scores ($\overline{X}$ NR=104.8 and $\overline{X}$ PR=94.5), as well as normal pediatric and neurological examination. All of the children in the NR group showed right handedness, while in the PR group all of the children, except for one were also right-handers.

Subjects were classified with the same instruments as in experiment 1: NBRD and RWAT. PR´s scores were below of 30 percentile for NBRD. Compared to the norms in the tests mentioned in experiment 1, PR's qualifications were between one and two standard deviations below those of the normals. For RWAT, PR's scores were below the expected level for their scholar grade.

The two groups of children did not show differences for chronological age ($p<0.65$), but their total IQ scores tended to be different: $F(1,19)=3.90$, $p<.06$. All parents of the participants gave informed consent.

Stimuli

Same as in experiment 1, linguistic variables were controlled developing a sentence corpus with well-known words according to a lexicographic dictionary, and validating the corpus in another group of children from the same community school, where the controls and PR came from (see experiment 1).

A total of 100 sentences 5-6 words long, were presented word by word on a computer monitor, with white colored letters on a black background. The words subtended a visual angle between 0.71 and 1.43 degrees. At the beginning of each sentence a fixation signal

("XXXXXX") was presented to indicate that the child was starting to read the sentence. Words' duration on screen was one second with an interstimulus interval of 0.5 second (stimulus onset asynchrony SOA 1.5 s).

Fifty sentences contained a syntactic violation (subject-verb number agreement violation): i.e. "Jaime vemos la television" (James watch television) while the other half had syntactically correct sentences: i.e. "Jaime ve la television" (James watches television). In order to homogenize the syntactic violation to be used, substitution of third person (singular) by third person (plural) was solely used in this paradigm.

Procedure

Children were instructed to read silently in order to decide whether the sentences were grammatically correct or not and to press a different mouse button in each case. Percentage of correct sentences and reaction times were evaluated.

Only correctly answered sentences were considered for analysis. Referential recordings (0.3-40 Hz bandpass) of ERP to the verb (located in the middle of the sentence) were obtained from 19 electrode sites (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz) of the 10-20 International System with a NeuroScan equipment.Linked earlobes were used as reference, with Ag/AgCl electrodes. The electro-oculogram (EOG) was recorded with bipolar electrodes placed at the outer cantus and the supraorbital ridge of the left eye.

The electrode impedance was always below 10 k . The sampling interval was 5 ms over a time epoch of 1280 ms, with a pre-stimulus baseline interval of 100 ms. EEG segments were visually edited to discard any artifact or EEG activity exceeded ± 50 µV.

Data Analysis

The electrophysiological data were the amplitudes of the early components (P150, N150 and P200) and P600. For the early components, mean amplitudes in the same latency windows and electrode locations as in experiment 1 were measured.

As the P600 is a slow, long-lasting response, mean amplitude values (relative to the average pre-stimulus baseline) of the ERP response to verbs were calculated on two time windows of 500-800 ms and 800-1100 ms.

The P600 effect (difference between ungrammatical and grammatical responses) was assessed by a 3-factor ANOVA with grammatical-ungrammatical, and antero-posterior (with 3 levels): Frontal (F3, Fz, F4), Central (C3, Cz, C4) and Parietal (P3, Pz, P4) and coronal (with 3 levels): Left lateral (F3, C3, P3), Midline (Fz, Cz, Pz) and Right lateral (F4, C4, P4) electrode placements as factors.

The group effect was assessed by a 3-factor ANCOVA (total IQ as covariable) with group, and antero-posterior and coronal electrode placements as factors.

We used an ANOVA for analysis of the behavioral results.

RESULTS

Behavioral Results

The PR group made significantly more errors identifying correctly the ungrammatical sentences, as revealed by percentage of correct responses: (Ungrammatical sentence: NR= 89.92% vs PR= 76.32%, $F(1, 20)=4.56$, $p<0.04$). PR also were significantly slower than controls in their reaction times (RT) when identifiying the grammatical correctness of sentences. For grammatical sentences we obtained in NR= 640 ms vs PR= 910 ms, $F(1, 20)= 4.79$, $p<0.04$), and the same tendency for ungrammatical sentences in NR = 670 ms vs PR= 870 ms, $F(1,20) = 2.47$, $p<0.13$).

ERP Results

Figures 4 and 5 illustrate the ERP for the syntactically correct (grammatical) and incorrect (ungrammatical) sentences in each group respectively, at 9 electrode sites.

It can be observed that brain electrical responses recorded for syntactic processing are very similar to those obtained during semantic processing (experiment 1). So, the ERP on anterior regions showed the N1-P2 complex while in posterior regions, the P150 followed by a broad negativity, and after these peaks, the so-called occipital P250. At all electrode sites, the early components were followed by the N400 that for the syntactic processing showed some distinct morphology compared to that recorded for the semantic processing. It may be caused by the position that the recorded word occupied in the sentence in each case: a middle position for the syntactic processing and the last position for the semantic processing. A broader morphology and larger amplitude of the N400 has been described for the last word of a sentence related to preceding words. After the N400, a slow and irregular positivity could be observed, lasting for some hundred of milliseconds, the P600 component.

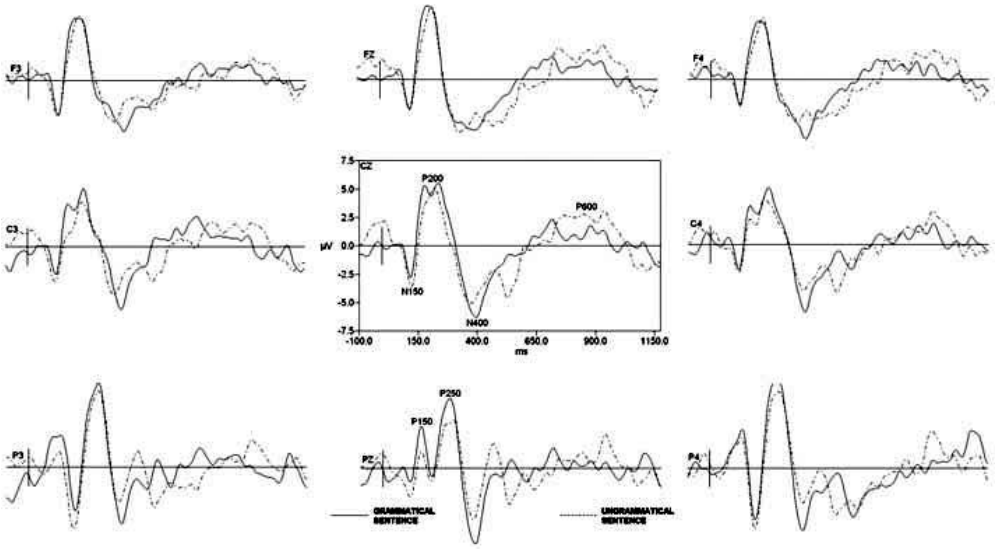

Figure 4. Grand average ERP to grammatical and ungrammatical sentences in the control (n=11) group in 9 electrode sites. Early components: N100, P200, P150, P250 as well as N400 and P600 components are marked. The P600 effect (larger P600 amplitudes for ungrammatical than for grammatical sentences) can be observed.

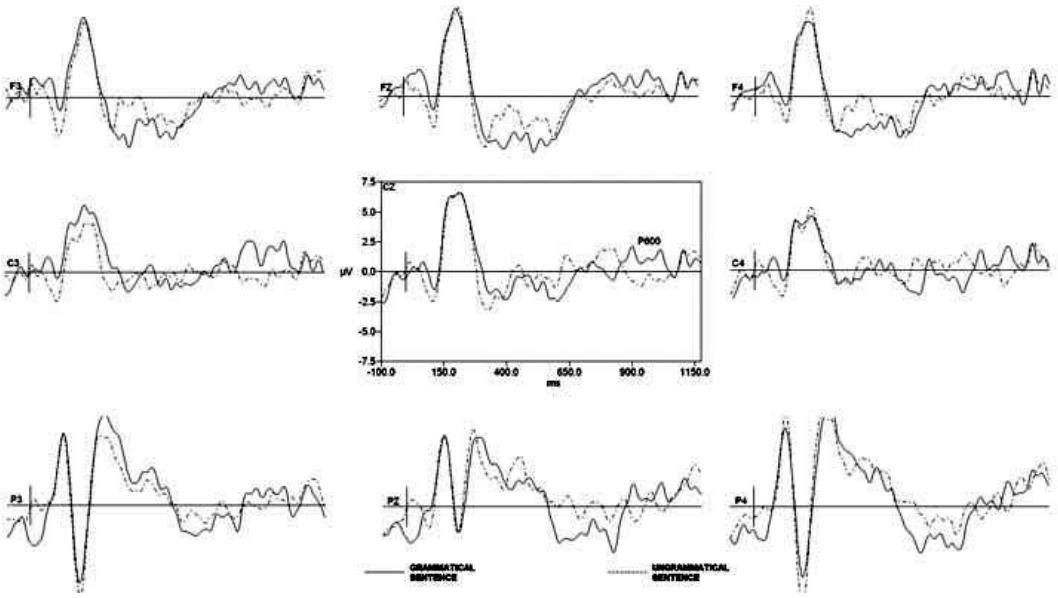

Figure 5. Grand average ERP to grammatical and ungrammatical sentences in the poor readers (n=11) in 9 electrode sites. No clear P600 effect can be observed.

Early Components

A tendency of larger P200 amplitude was observed in PR with respect to controls, that - perhaps because of the relative small size of this sample - did not show statistically significant effects.

As in the experiment of semantic processing, we interpreted this finding as a greater effort of attention for decodification of words in these children, as compared to normal readers.

P600 Component

Effect of Syntactic Anomaly

Clear differences in ERP responses to grammatical and ungrammatical sentences were obtained in the control group yielding to the so called P600 effect, that is greater positivity for ungrammatical than to grammatical sentences (see figure 4).

As figure 4 shows, P600 effect is better observed at frontal and central leads with no lateralization effect.

For the PR group, we did not find P600 effect, since the positive response was similar for both types of sentences (see figure 5).

Group Effect

The control group showed significantly greater P600 amplitude in the time window of 800-1100 ms than PR group, for ungrammatical sentences (see figure 6): Group main effect

F(1,18)= 11.08 p<.003. This greater P600 amplitude of the controls can be observed in every lead illustrated in figure 6 (i.e. central, parietal and frontal leads).

A topographical ANOVA of the P600 effect was done using the scaled values (McCarthy and Wood, 1985) of the P600 effect obtained by subtraction of the response of grammatical sentences to that of the ungrammatical ones, in the time window of 800-1100 ms. Between-group differences showed that scaled P600 effect was larger for controls respect to PR in central, and frontal leads. This finding points out that P600 effect was larger for controls respect to PR in those regions where the effect seems to be maximum in normal children. The analysis reveals an effect of lateralization for P600, too. It was found a main effect of hemisphere that points out to a larger effect in right derivations respect to the left ones without a significant interaction by group.

As for the semantic processing, PR children seem to have also deficiences in syntactic-semantic reanalysis attributed to P600 elicited for the sentences presented in this experiment.

The behavioral results supported the electrophysiological findings. The failure of the PR to show a syntactic-semantic analysis like their control peers was also evidenced in their behavioral responses, as they demonstrated a greater number of errors in the identification of ungrammatical sentences and in the reaction times employed to identificate both grammatical and ungrammatical sentences.

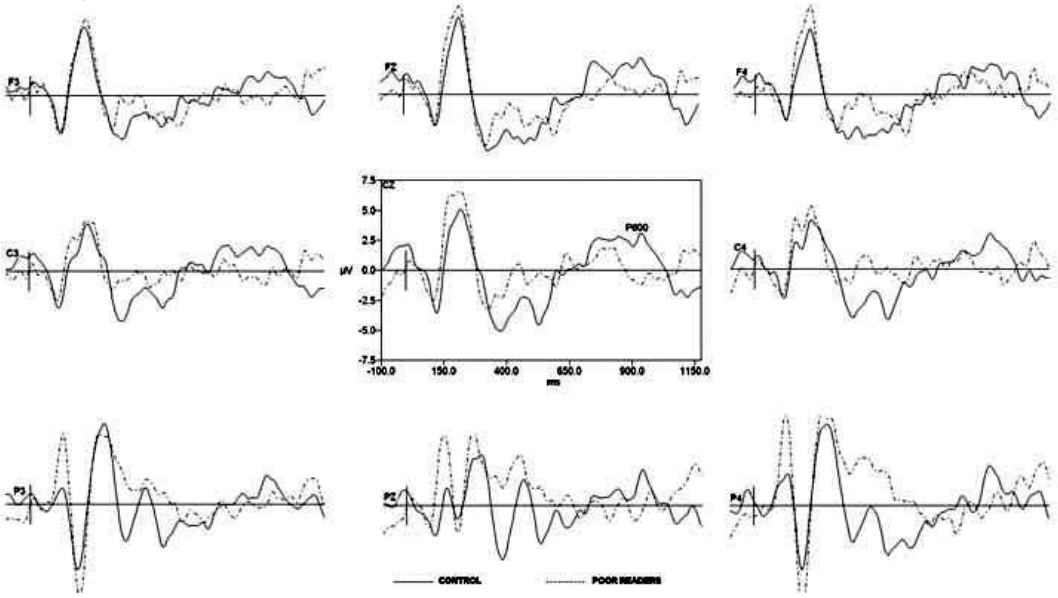

Figure 6. Grand average ERP to ungrammatical sentences in the control (solid line) and the PR (dashed line) groups. Larger amplitudes of the P600 component for control than for poor readers can be observed at all electrode sites.

GENERAL DISCUSSION

Semantic Processing

In the control group every child exhibited an increase of the N400 amplitude in response to semantically incongruous endings. This N400 effect is in accordance with findings of

previous reports on normal children (Holcomb et al., 1992; see also Hahne et al., 2004 for auditory sentences) and on language-impaired children (Neville et al., 1993). Both groups showed an N400-like response to both sentence types, although this response was larger for incongruent sentences.

Nonetheless, the grand average of the PR group showed the same response to congruent as to incongruent sentences, thus no N400 effect was detectable.

Clear differences between normal and PR children during the semantic processing were shown in this study. PR children showed smaller N400 amplitude for incongruent sentences with respect to normal children. This was interpreted as an electrophysiological sign of deficiency in lexical integration.

As mentioned, lexical integration is a complex process that entails the successive lexical access of each word of a sentence along with the construction of a mental model containing specific data of the sentence in terms of syntactic, semantic and pragmatic information. At the end of this process specific meaning contained in the sentence will emerge.

It is obvious that this lexical integration process involves both the linguistic and memory functions that work together to success in the extraction of meaning. So, a deficiency in lexical integration process reflected in the electrophysiological response of PR, could stem from failures in one or several of the following stages: a) search in the internal lexicon for each word (see below), b) temporal construction of context, given by the successive words in the sentence, c) whole mental representation of the context where meaning extraction takes place.

On the other hand, these electrophysiological results were positively related to the behavioral ones, as the reduced N400 amplitude was in line with the behavioral measure of a poorer performance in the identification of sentence congruence, since PR exhibited more errors than controls in this task.

Smaller N400 amplitudes of the PR could be a sign of their deficit in lexical integration process. Thus, PR might be characterized by a reduced function of the networks involved in the lexical integration process, which would be mirrored in reduced amplitude of N400. This deficit could also be seen as a more superficial lexical integration processing of PR than a more comprehensive one of the control children. A general interpretation of N400 is that it reflects a neural search through the internal lexicon, as a stage of the process of recognizing the meaning of a word, (Nobre and McCarthy, 1995; Holcomb, 1993; Van Petten and Kutas, 1987).Thus, a reduced N400 amplitude could be the sign of a slight, incomplete or inefficient search, leading to a deficient reading comprehension.

This inefficient lexical search could be the consequence of deficiencies in early mechanisms of codification of words, seen in the larger amplitudes of the P200 exhibited by PR, as Silva-Pereyra et al. (2003) found in a word categorization task. They described that PR have deficiencies very early in the processing of words, reflected in larger P200 amplitudes, but finally performed the semantic task as efficiently as normals, mirrored in normal N400 responses. In this way, presumed deficits at semantic level might be consequence of early codification deficits.

The controversy between a semantic deficit per se or as a consequence of early word processing was continued in the differences obtained between the results of experiment 1 of this chapter and those of Rodríguez et al. (2005). With a similar paradigm of stimulation, in the later study, PR showed clearly larger amplitudes of all of the early components (P150,

N150 and P200) compared to normal children. In experiment 1, we only obtained a discrete effect only for P200 component.

A possible explanation could be the heterogeneity of characteristics of reading abilities that can be found in PR samples, as we have mentioned in the introduction. Alternatively, the deficiency in semantic processing evidenced in the diminished N400 response could not be a simple consequence of deficits in early codification process, but constitute a semantic deficit per se. This hypothesis may be extended to the findings in experiment 2 of syntactic processing, where we found a similar ERP pattern with no group-differences in early codification process but evidence of a poor syntactic-semantic processing of the PR. More electrophysiological studies with well characterized PR samples are needed to advance a solution for this question.

Furthermore, the finding in this sample of PR is the opposite of that reported for Language-Impaired (LI) children (Neville et al., 1993) and dyslexic adults (Robichon et al., 2002) (that means a large N400 amplitude of the disabled groups as compared to controls). Thus, LI and dyslexic children display "compensatory increases in the effort required to integrate words into context" reflected in large N400 amplitudes; while PR –that supposedly show milder reading difficulties than LI or dyslexics –show smaller amplitude of the N400 component as a sign of an inefficient lexical integration process.

Our results on N400 amplitude are similar to those of Stelmack's group which working with priming paradigms have consistently reported a smaller N400 of RD children who are described as deficient in Reading and Spelling tests and having similar cognitive characteristics as the PR of our study (Stelmack et al. 1988; Stelmack and Miles, 1990; Miles and Stelmack, 1994; Greenham et al., 2003).

The above mentioned results provide evidence that PR and dyslexics are qualitatively distinct groups in semantic processing of reading.

Syntactic Processing

The presence of the P600 component in normal reading children was clearly demonstrated. As described for adults, in response to a syntactic anomaly detected in a sentence (violation of subject-verb agreement) normal children displayed a P600 effect (Hagoort et al., 1993; Osterhout and Mobley, 1995). This result is also partially similar to that reported by Hahne et al. (2004) in children tested with auditory sentences. They described a P600 effect for children since the age of 7, although their figure only shows the effect for parietal sites with no sign of a developmental change in topography, that could be related to those linguisitc changes of early and late childhood involved in the syntactic-semantic processing mirrored in P600. We hope to see the "gradually develop toward adult-like processing" reflected in electrophysiological form.

We would like to add a commentary on the comparison between the P600 reported in the literature for adults and that obtained for children. The P600 of normal children showed different characteristics to those reported for adult subjects. First, we observed a distinct latency for the P600 effect: for adults it has been reported in the time window between 500-800 ms, and for our normal children the P600 effect was present until 800-1100 ms. Although it is difficult to compare, the latencies reported in children by Hahne and her colleagues (2004) in their developmental study, are similar to those of our study. This latency delay

might imply that children carried out the syntactic-semantic analysis associated with P600 in a time window that comes later than that reported for adults, which may be explained by the lack of experience in reading that children have. Second, unlike the reports for adult subjects, the topography of P600 shown in normal children was fronto-central with some lateralization to the right hemisphere, instead of the centroparietal distribution with lateralization to the right hemisphere that have been described for adults (Osterhout and Holcomb, 1992; but see Hagoort et al., 1993). Although a centroparietal topography could be due to the motor response imposed to the children, some studies on adults that used a motor response for identyfing the type of sentence, have not reported such topographical distribution (Hagoort et al., 1993). Our interpretation of this fact is that it might be due to a maturation effect. This effect may imply that in normal children (9-12 years old) the process of syntactic-semantic reanalysis - related to P600 - is a controlled process that requires attention and depends fundamentally on frontal function. Nonetheless, other authors do not described changes of P600 topography in children related to changes in linguistic strategies involved in syntactic analysis (Hahne et al., 2004).

The longer latency of P600 effect and its frontocentral distribution in normal children might point out that the syntactic-semantic reanalysis to which this component has been functionally related is a process still inmature in children at this age. A limited experience with reading that children of this age and socioeconomic status usually have, may explain these differences, although it is undeniable that we need more electrophysiological studies about language development before any conclusion can be drawn.

However, it was possible to demonstrate from the electrophysiological point of view, that syntactic-semantic reanalysis represented by P600 was different for each group of children studied here. Thus, PR children did not displayed electrophysiological signs that may suggest a distinct processing for ungrammatical than for grammatical sentences, showing in this manner a deficient syntactic-semantic processing as compared to their control peers. These results agree with those reported by Avecilla-Ramírez et al. (2004) in PR children during an acceptability judgment task. They considered that this smaller P600 effect in PR was due to deficits in the regulation of working memory process that come into action while reading sentences.

The lack of P600 effect in PR points to the fact that the syntactic processing carried out by these children does not differentiated between grammatical and ungrammatical sentences. It seems that this processing is the same for both types of sententes which can be interpreted as a reflection of a poor syntactic analysis, or a deficient syntactic-semantic reanalysis depending on the functional interpretation given to P600.

Our interpretation is that the linguistic processing reflected in P600 in case of our sentences is preferently a syntactic-semantic reanalysis. Unlike studies designed to probe hypothesis in modular models (see for example, Hahne and Friederici, 1999), other investigations allow to find a closer relation between P600 and the syntactic-semantic reanalysis. Such investigations have used sentences with syntactic violations where a meaning can be “rescued” (with real words) comparing their electrophysiological responses with those of semantically inoperant sentences (using pseudowords or jabberwocky sentences). In general a LAN effect is described in both types of sentences, but the P600 effect was only found in the meaningful sentences (Münte, Matzke, Johannes, 1997; Canseco-González et al., 1997; Münte et al., 1998).

According to the explanation given above, we described the lack of P600 effect as a deficient syntactic-semantic analysis in this sample of PR.

On the other hand, to our knowledge there are no electrophysiological studies of P600 in dyslexics or reading-disabled populations, so then at the moment it is not possible to compare the results of the present study.

The lack of P600 effect shown by PR might be seen as an electrophysiological sign of a syntactic-semantic processing deficiency that only has been reported for behavioral measures.

CONCLUSION

The studies that we have described provide some neurobiological bases of the problems in semantic and syntactic processing in children with learning disabilities, especially reading difficulties, giving evidence of such deficits at the physiological level, besides the behavioral level.

ACKNOWLEDGEMENTS

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Chapter 10

EARLY DETECTION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER. THE EARLY CHILDHOOD INVENTORY-4 SCREENING IN MEXICAN PRESCHOOL CHILDREN

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ABSTRACT

Purpose of study was to examine prospectively usefulness of Early Childhood Inventory-4 (ECI-4) in identifying Attention deficit hyperactivity disorder (ADHD) in a sample of children < 6 years of age who were evaluated in school settings and compare results with those of Conners Rating Scales-Revised (CRS-R) 6 months later. Sample consisted of 34 healthy children (20 boys, 14 girls) prospectively followed-up. Frequency of children fulfill ADHD criteria in ECI-4 parent scale was 17%, and in teacher scale was 32%. Frequency of children fulfill ADHD criteria in parent CRS-R was 20%, and for teacher questionnaire was 23%. Correlations were significant among teacher ECI-4 and both teacher and parent CRS-R scales. Sensitivity and specificity of teacher and parent ECI-4 scales were not good. In summary these facts support partially the use of ECI-4 screening of ADHD in Spanish–speaking preschool children.

Key Words: Attention Deficit-Hyperactivity Disorder, Preschool children, Screening

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INTRODUCTION

Although specific aspects of the definition have changed over time, certain features of this disability have remained essentially the same. The majority of definitions recognize motor restlessness, short attention span, and impulsivity as the basic features of this disorder (Poblano *et al*., 1994). Attention deficit hyperactivity disorder (ADHD) is more prevalent in males (3:1or 10:1) than in females (Levy *et al*., 2005). ADHD debilitates many aspects of an individual's life, including academic activities, social skills, and the parent-child relationship. Recent studies suggest that 30-60% of affected individuals continue to show significant symptoms of the disorder into adulthood (Harpin, 2005). Children with the disorder are at greater risk for long-term negative outcomes and disability such as lower educational and employment attainment and higher prevalence of alcohol or drug intake. The objective of this study was to examine clinical usefulness of the ECI-4 in identifying prospectively screening for ADHD among children < 6 years of age who were evaluated in school settings and to compare results with those of Conners Rating Scale-Revised (CRS-R) (Conners, 1999) at least 6 months later in a sample of preschool children in Mexico City.

DEFINITION

First, ADHD is an alteration whose cardinal symptoms are inattention, hyperactivity, and impulsivity. Second, the majority of experts believe that ADHD is a developmental disorder characterized by a consistent and chronic pattern of atypical behavior. Third, ADHD begins early in life with impairing symptoms exhibited during preschool years or first grade. Fourth certain environmental characteristics highlight the severity of the disability, for example at a party or in the classroom. And fifth, the severity of certain symptoms appear to change over time and the disorder seems to be less symptomatic in adolescents than in young children (American Psychiatric Association, 1987; American Psychiatric Association, 1994; Poblano *et al*., 1994).

CLASSIFICATION

In the Diagnostic and Statistical Manual [of Mental Disorders], Fourth Edition (DSM-IV*)*, three subtypes of ADHD are distinguished on the basis of two dimensions of symptoms: 1) the inattention dimension that includes difficulties in sustaining attention, distractibility, lack of task persistence, and disorganization, and 2) the hyperactivity-impulsivity dimension that includes excessive motor activity and impulsive responding. There are three subtypes of ADHD that are based on the different patterns of deviance found in these two dimensions of symptoms as follows: 1) the combined type exhibits maladaptive levels of both inattention and hyperactivity-impulsivity; 2) the predominantly inattentive type corresponds to the Diagnostic and Statistical Manual [of Mental Disorders], Third Edition (DSM-III*)*definition of attention deficit disorder without hyperactivity by exhibiting maladaptive levels of inattention, but not hyperactivity-impulsivity, and 3) the predominantly hyperactive-impulsive type is defined on the basis of maladaptive levels of activity.

DSM-IV lists nine inattention symptoms, six of which must be present for at least 6 months, -and at a level that is troublesome for a child to meet the criteria. The DSM-IV lists six hyperactivity symptoms and three impulsivity symptoms, at least six of which must be present for at least 6 months at a level that is inappropriate (Table I).

Table 1. Criteria for the Diagnosis of ADHD

Criteria for the Diagnosis of AD-HD *
The diagnosis requires evidence of inattention or hyperactivity and impulsivity or both. Inattention. Six or more of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent whit developmental level. • Often fails to give close attention to details and makes careless mistakes • Often has difficulty sustaining attention • Often does not seem to listen • Often does not seem to follow through • Often has difficulty organizing task • Often avoids task that require sustained attention • Often loses things necessary for activities • Often is easily distracted • Often is forgetful Hyperactivity and impulsivity Six or more of the followings symptoms of the hyperactivity and impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent whit developmental level. • Often fidgets • Often leaves seat • Often runs about or climbs excessively • Often as difficulty with quiet leisure activities • Often is “on the go” or “driven by motor” • Often talks excessively • Often blurts out answers • Often has difficulty awaiting turn • Often interrupts or intrudes Symptoms that cause impairment: • Are present before 7 years old • Are present two or more settings (e.g. home, school, or work) • Do not occur excessively during the curse of a pervasive developmental disorder, schizophrenia, or another psychiatric disorder • Are not better accounted for by another mental disorder (e.g. a mood disorder or an anxiety disorder)

The criteria are adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised 2000.

For all types of ADHD, the DSM-IV lists the following several additional criteria: 1) onset must be by age 7 years; 2) symptoms must cause difficulties in at least two settings (e.g., school, home); 3) symptoms cause clinically significant impairment in functioning, and 4) symptoms are not due to other psychiatric disorders in children (e.g., pervasive developmental disorder, schizophrenia, mood or anxiety disorder).

EPIDEMIOLOGY

In children, ADHD is known as a common condition: the prevalence of hyperkinetic disorder in 7-year-old boys in an British city was 1.5% (Taylor *et al*., 1991). A community sample from Puerto Rico of children < 11 years of age yielded a prevalence of 6.7% (Bird *et al*., 1988), while prevalence in an American pediatric population was 9.5% (Costelo *et al*, 1988); in a German survey of elementary school children, prevalence was 17.8% (Baumgaertel *et al*., 1995). Although no prevalence studies of ADHD have been performed in Mexico, earlier work by García-Pedroza *et al*. (1983) showed a 19.6% prevalence of minimal brain dysfunction in 9-year-old school children from the Tlalpan Delegation in Mexico City while they performed a search for epileptic children. At present, ADHD is the first cause of pediatric mental health care consultation in psychiatric hospitals in Mexico City (Poblano *et al*., 2005).

PATHO-PHYSIOLOGY

Attention has been drawn to the role of adverse perinatal events in the development of neuro-psychiatric difficulties. At present, the relationship between perinatal risk factors and ADHD is becoming stronger. The majority of prospective studies deal with selected high-risk populations; these indicate an increased risk of ADHD for high-risk neonates (Hadders-Algra *et al*., 1988; Barrera-Reyes, 2003). Infants who acquire brain damage may develop different brain rewiring; this might lead to a variety of behavioral sequelae, with signs of neurologic dysfunction that implicate dysregulation of cathecholaminergic systems that might lead to develop inappropriate behavior.

On the other hand, there is consistent evidence from family, twin, and adoption studies that ADHD is familial and genetically influenced (Biederman *et al*., 1986; Thapar *et al*., 2000). There is now a great international effort focused on attempting to identify susceptibility genes for the disorder and related traits. Molecular genetic studies of ADHD have focused on genes in catecholaminergic pathways because theoretic considerations and the effectiveness of stimulant treatment implicate a catecholaminergic dysfunction. The dopamine D_4 receptor gene has been examined in many studies. Although behavioral disorders are likely to be mediated by many genes acting in concert, researchers have examined with good results the association between ADHD and the dopamine D_4 receptor gene as putative gene in the disorder (Faraone *et al*., 2001).

HEALTH CARE COSTS

Healthcare costs for individuals with ADHD in the United States of America suggests that there are increased costs compared with age-matched controls. A population-based historical cohort study followed 4,880 individuals from 1987-1995 and compared at the ninth year for medical costs per person: ADHD medical costs were $4,306 U.S. dollars (USD), whereas non-ADHD medical costs were $1,944 (USD) (Harpin, 2005).

In Mexico National Institute of Informatics, Geography, and Statistics (INEGI) 2000 data showed that the pediatric population between 5 and -15 years of age reached 21,951,816 subjects (National Institute of Geography, Statistics and Informatics, 2000 [Mexico]). A conservative calculation of the Mexican pediatric population from 5-15-year of age with ADHD, considering a 10% prevalence is 2,195,182 individuals. At a cost of $25 USD for a first-time medical appointment for all individuals with ADHD, the cost for initial identification of the disorder would be approximately $54,879,550 USD; the same amount must be spent for 1-week therapeutic intervention (three 1-hour sessions). In the case of methylphenidate use and considering the cost of presentation as $17.21 USD, pharmacologic treatment for all persons with ADHD would be $37,779,082 USD; comparative data of costs in Mexican pesos is shown in Table II. Nonetheless, the most important problem is that many persons in Mexico find their life's goals and expectations limited due to a disorder that technically can be identified easily.

Table 2. Estimated costs for initiating health-care in 2,195,182 Mexican children with ADHD in U.S. dollars (USD) an Mexican pesos.

	Mexican pesos	U.S. dollars
• First time medical appointment	$658,554,600	$54,879,550
• Speech therapy (three sessions per week)	$658,554,600	$54,879,550
• Pharmacologic treatment	$434,646,036	$37,779,082
Total	**$1,751,755,236**	**$147,538,182**

EARLY IDENTIFICATION

The earliest possible identification of children who exhibit serious developmental disabilities such as ADHD is an important goal of students of human development. Timely identification of these individuals is crucial for a number of distinct clinical, educational, and social objectives. These include the need to identify the etiology of the disability, to improve management, to institute early remedial measures, to develop more specific and effective methods for such remedial interventions, and to direct and mobilize societal resources to deal more effectively with the objectives of primary and secondary prevention of developmental disability.

Many efforts have been made concerning early identification of ADHD. The first procedure for early identification is application of DSM-IV questionnaires, however, certain

limitations focus on the low sensitivity of the instrument due to the higher levels of motor activity in this age group. Lahey *et al.* (1998) studied a group of children for 4-6-years of age who met DSM-IV criteria for each subtype of ADHD; they concluded that when children with ADHD were diagnosed by means of a structured diagnostic protocol, all three subtypes are valid. Nearly all children who met full criteria for ADHD over the subsequent 3 years continued to display marked functional impairment relative to comparison children (Lahey *et al.*, 2004). DuPaul *et al.* (2001) studied a sample of 94 children between 3 and 5 years of age with regard to, their family functioning, medical functioning, parent-child interactions, and classroom behavior. They report that young children with ADHD exhibited more problem behavior and were less socially skilled than their normal counterparts. An other way to identify preschool children with ADHD has been to develop new screening instruments, such as the Early Childhood Inventory-4 (ECI-4). Gadow and Nolan (used this inventory to ascertain that ADHD + Oppositional defiant disorder (ODD) in preschool children were largely additive rather than existing solely as entities. In general, the ODD+ADHD group received the highest ratings of severity of symptoms, difficulties with peers, and developmental deficits.

EARLY DETECTION OF ADHD IN MEXICAN PRESCHOOL CHILDREN

The sample consisted of 34 healthy children invited for participate from different regular schools and classes of the southern area of Mexico City (20 boys, 14 girls) who were prospectively followed-up, Early Childhood Inventory-4 (ECI-4) screening was performed first and Conners Rating Scales (CRS) were tested 6 months later when children were > 6 years of age. When examined for the first time, the children were 5 years of age (mean = 67.83 months, SD = 0.77 months), teacher time knowing children was 6.8 months, SD 9 months, and teacher time spent with children was 5.7 h/day SD 1.13 h/day. Inclusion criteria were: Preschool children between 66 and 71 months of age with regular school attendance. Exclusion criteria were: Deafness and blindness, epilepsy, congenital malformations, and genetic syndromes.

ECI-4 materials were send to parents and teachers of potential patients by school principals included rating scales, background information questionnaires, and consent documents. Parents and teachers were required to complete and return their forms anonymously but respondents indicated age, gender, and relationship to child. In the majority of cases (88%), ratings were completed by the child's mother. Six months later Parents and Teachers CRS were sent in the same manner, and results between ECI-4 and CRS were compared. Clinical diagnoses derived from structured psychiatric interview in a research-oriented teaching hospital setting in appropriate cases at the end of the study.

The parent version of the ECI-4 contains 108 items, which correspond to the DSM-IV. Individual items are scored in two ways: Symptom count (binomial), and symptom severity (semi-quantitative). For symptom count scores, a specific symptom is generally considered to be a clinically relevant problem if rated as occurring often or very often (0 = never/sometimes or, 1 = often/very often). When symptom count score is = or > number of symptoms specified by DSM-IV as necessary for diagnosis of possibility, the child receives a screening cutoff of “yes” for the disorder, nonetheless this does not signify a clinical diagnosis. For symptom

severity scores, items are scored 0 = never, 1 = sometimes, 2 = often, and 3 = very often. Scores for each item are added together to generate a symptom severity score for each symptom category and for all items (total severity score). ECI-4 symptom categories are as follows: Attention deficit disorder-Inattention (nine items), Attention deficit disorder-Hyperactivity (nine items); Oppositional defiant disorder (eight items); Conduct disorder (10 items); Generalized anxiety disorder (nine items); Social phobia (two items); Separation anxiety disorder (eight items, parents only); Major depressive disorder (11 items); Dysthymic disorder (eight items); Autistic disorder (12 items), and Asperger's disorder (eight items). The teacher version of the ECI-4 contains 87 items from the parent version, but excludes symptoms not likely to be observed in the school setting (Gadow and Sprafkin, 2000a; Gadow and Sprafkin, 2000b).

The long version of the Conners Rating Scale-Revised was used, the parent version contains 80 items, and the teacher version contains 59 items. Both scales were rated as ECI-4 was rated for further statistical comparisons. For symptom severity scores, items are scored 0 = never, 1 = sometimes, 2 = often, and 3 = very often. Each scale was rated as occurring often or very often (0 = never/sometimes or, 1 = often/very often). When symptom count score is = or > number of symptoms specified by DSM-IV as being necessary for diagnosis of possibility, the child receives a screening cutoff of “yes” for the disorder, but this does not necessarily comprise a clinical diagnosis (Conners *et al.*, 1998a; Conners *et al.*, 1998b).

RESULTS

Data from parent and teacher responders to the ECI-4 screening scale in the sample (n = 34) are shown in Table 3; frequency of children fulfill criteria for AD-HD in ECI-4 parent scale was 17%, and in teacher scale was 32%. Correlation between symptom severity scores in parent and teacher ECI-4 scales was significant (rho = 0.372, p = 0.017). Questions most frequently answered positively for children with AD-HD in parent questionnaire was: “runs about or climbs on things when asked not to do so” (10 often/1 very often). Questions most frequently answer positively for children with AD-HD in teacher questionnaire was: “has difficulty organizing task and activities” (8 often/4 very often), “is easily distracted by other things going on” (7 often/8 very often), “is forgetful in daily activities” (11 often/2 very often), “runs about or climbs on things when asked not to do so” (8 often/4 very often), and “talks excessively” (8 often/3 very often).

Results of parent and teacher CRS-R are shown Table 4; frequency of children fulfill criteria for AD-HD in parent questionnaire was 20%, and for teacher questionnaire, 23%. Correlation between symptom severity scores in parent and teacher CRS-R was also significant (rho = 0.402, p = 0.018).

At last the study four children were diagnosed as having AD-HD, three of them with predominance of hyperactivity and one with combined type. Correlations among symptom severity scores ECI-4 scales and CRS-R were significant except between parent ECI-4 and teacher CRS-R and among parent ECI-4 and parent CRS-R (see Table 5). Sensitivity and specificity of teacher and parent ECI-4 scales was compared with the neuropsychiatric interview, parent ECI-4 scale had sensitivity of 0.60, specificity was 0.51; teacher ECI-4 scale has sensitivity of 0.78 while specificity was 0.56 (Poblano and Romero, 2005).

Table 3. Frequency and Percentage of Attention-Deficit/Hyperactivity Disorder, Oppositional-Defiant Disorder and Conduct Disorder Identified by Symptom Count in a Sample of 34 Preschoolers Using Early Childhood Inventory-4 Screening

	Parent ECI-4	Teacher ECI-4	Agreement
ADHD	6 (17.6)	11 (32.3)	4 (11.7)
Oppositional disorder	2 (5.8)	6 (17.6)	1 (2.9)
Conduct disorder	-	5 (14.7)	-

Table 4. Frequency and Percentage of Attention-Deficit/Hyperactivity Disorder, Oppositional-Defiant Disorder and Conduct Disorder Identified by Symptom Count in the Sample of 34 Preschoolers Using Conners Rating Scales-Revised Examination

	Parent Conners Rating-Revised scale	Teacher Conners Rating Scale-Revised	Agreement
ADHD	7 (20.5)	8 (23.5)	4 (11.7)
Oppositional disorder	6 (17.6)	6 (17.6)	3 (8.8)
Conduct disorder	1 (2.9)	3 (8.8)	1 (2.9)

Table 5. Correlation of Parent and Teacher Ratings of Attention-Deficit/Hyperactivity Disorder on the Early Childhood Inventory-4 and the Conners Rating Scales-Revised in a sample of 34 Preschool children

	Parent ECI-4	Teacher ECI-4	Parent CRS-R	Teacher CRS-R
Parent ECI-4				
Teacher ECI-4	0.372 (0.017)			
Parent CRS-R	0.337 (0.052)	0.581 (0.001)		
Teacher CRS-R	0.107 (0.547)	0.654 (0.001)	0.403 (0.018)	

COMMENTS

Significant correlations were found between teacher versions of the ECI-4 and CRS, but not between the parents version of the two scales. These findings support partially the use of the teacher ECI-4 to screen for ADHD in Spanish-speaking preschool children; use of the parents version of the ECI-4 as a screening test requires more supporting evidence. Frequencies of ADHD in our sample are high compared to other studies, which may reflect a bias of selection (parents of children with AD-HD may be more likely to participate).

There are large literature on the convergence and divergence of parent and teacher ratings of ADHD. Differences between symptoms groups varied depending on how they were configured (teacher versus parent ratings) and settings (clinic versus community). Symptoms are most apparent for teachers-defined groups in community samples (as in our results) and parents-defined groups in clinic samples (Gadow and Nolan, 2002). These observations can be attributed to the fact that children with ADHD exhibited more negative social behavior in school settings and scored significantly lower for teacher' scales.

Sensitivity is defined as the capacity to differentiate between children with the disorder from those without the disorder, while specificity is better defined as the ability to differentiate children without the disorder from children with the disorder. Measures of sensitivity and specificity in our study were not good, and support only partially the use of ECI-4 for ADHD screening when compared with psychiatric interview (Sprafkin et al., 2002).

Early detection of ADHD is very convenient. The last revision of the DSM-IV criteria for ADHD included an age-of-onset criterion requiring that symptoms be present prior to the age of 7 years (American Psychiatric Association, 1994). The validity of very early ADHD diagnoses is open to debate. However, reports find that the majority of children with diagnosis of ADHD first exhibited symptoms in early childhood (Willoughby et al., 2000; Gadow et al., 2000; Gadow and Nolan, 2002; Keenan and Wakschlag, 2002). In this sense ECI-4 screening can be useful for early detection of ADHD in Spanish-speaking children. This study suggests the usefulness of continued study for application of this instrument. Results from this study support partially the validity of the teacher's ECI-4 as a screening tool for ADHD in this age group.

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