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Regional cerebral blood flow correlates of orthographic analysis and phonetic discrimination in adults who were reading-disabled as children

Flowers, Donna Lynn, Ph.D.

The University of North Carolina at Greensboro, 1989

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REGIONAL CEREBRAL BLOOD FLOW CORRELATES OF ORTHOGRAPHIC ANALYSIS AND PHONETIC DISCRIMINATION IN ADULTS WHO WERE READING DISABLED AS CHILDREN

by

Donna Lynn Flowers

A Dissertation Submitted to
the Faculty of the Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

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1989

Approved by

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APPROVAL PAGE

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This research study was undertaken to test a model of posterior displacement of focal perisylvian activation based on the autopsy work of Galaburda, the intraoperative work of Ojemann and Rasmussen, and neural developmental animal work. By this model, an early lesion in Wernicke's area would displace some aspects of the neuronal processing capacity originally destined for Wernicke's area to adjacent, posterior cites.

Forty-one normal adult males and 47 adult males with documented childhood reading evaluations (the Orton group) performed an orthographic analysis (spelling) task. Some also did phonetic and tonal tasks. Regional cerebral blood flow was measured during task performance using the 133-Xenon inhalation method. Normal subjects showed cerebral activation at left Wernicke's area proportional to spelling task accuracy, while Orton subjects showed activation both at Wernicke's area and at the left angular gyrus such that better performers of the spelling task activated Wernicke's area more and angular gyrus less. An inverse relationship between childhood reading impairment and angular gyrus activity also was found, and this was independent of either task accuracy or adult reading attainment.

The phonetic task, controlled by tone task activation, did not elicit cerebral blood flow activation which was related to phonetic task performance. Using either phonetic or tone task flow as a control for spelling task activation, however, it was shown that the spelling task results could not be explained in terms of phonetic or tone processing.

Since the phonetic component was unrelated to childhood reading history, and since neither the phonetic nor the tone task flows could eliminate the relationship between angular gyrus flow and spelling task activation, it was concluded that (1) the relatively posterior displacement of activation in the spelling task is of a non-phonetic processing component, and (2) that this is consistent with a persisting, mild deficit in Wernicke's area.

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CHAPTER 1

INTRODUCTION

Dyslexia, or developmental reading disability (RD), is said to be present when a child of adequate intelligence and opportunity does not achieve expected reading skills in spite of apparent organic and emotional health. The etiology of RD remains controversial; indeed, it is unlikely that a single explanation will be sufficient. Nonetheless, several lines of evidence suggest that a persisting dysfunction is present, at least in some reading disabled individuals. The first suggestion of this is purely behavioral: language deficits are consistently found to continue into adulthood and, tasks which distinguish dyslexic children from others also distinguish adults with a history of reading disability from others, regardless of their eventual reading achievement. In addition, there is evidence which suggests a neural dysfunction: left hemisphere neural anomalies, believed to have been formed _in utero_, have been identified in dyslexic adults.

Basic to neural deficit models of dyslexia is that, for nearly all right handers and most left handers, many functions essential to efficient verbal processing are mediated by localized regions or networks of the left hemisphere. There is wide support for this from observations that specific left hemisphere lesions selectively effect acquired language skills. These observations led Broca, and later Wernicke, to identify what are now classically known as the anterior and posterior language areas of the left hemisphere.

Behavioral and physiological studies, reviewed below, have provided further verification of left hemisphere involvement in language functions. Some of these yield contrasting results in dyslexic individuals. But, the most cogent evidence for an impaired left posterior substrate in RD is based on the post hoc correspondence between reading disability and a left hemisphere structural abnormality. That is, atypical neuroanatomy has been observed in static brain images of dyslexic subjects, and neuronal ectopias and dysplasias have been described in the left temporal lobes of dyslexic brains scrutinized at autopsy.

Since direct observation of functional language areas is not possible, brain/behavior correlates of dyslexia have necessarily been measured indirectly using physiological techniques. Several techniques have been considered appropriate - event-related potentials (ERPs), positron emission tomography (PET), and regional cerebral blood flow (rCBF).

The present investigation employed the 133-Xenon inhalation rCBF technique to measure cortical activity in normal, adult male subjects and male adults with documented childhood reading deficiencies. A neural displacement hypothesis of dyslexia was tested using two types of auditory verbal tasks and a tone discrimination task. The results are discussed in terms of a neural displacement model.

Structural Basis for Reading Disability

Morphology of Language Regions

Underlying structural differences in the language areas of normal human subjects were first reported by Geschwind and Levitsky (1968). They found the left planum temporale (Tp) to be longer in 65 of the 100 normal brains they studied. This finding has been replicated and extended by others and includes infants as well as adults (see Strauss, Kosaka and Wada, 1983, for a review). Geschwind and Levitsky also found that 57 of their specimens showed a sharper backward slope of the left Sylvian fissure which extended more posteriorly. Differences in the accompanying middle cerebral artery configuration could be seen by the unaided eye. Not only autopsy examinations but also CT scans of living brains show gross morphologic asymmetries. Differences reported by LeMay and Kido (1978) are: different length and height of the Sylvian fissure in right handers; a wider, more forward right frontal lobe; and a higher incidence of either reversed asymmetry or a lack of asymmetry in left handers.

It is interesting to note that right-left differences in the language areas are normally present prenatally and in the infant before language acquisition (Strauss et al, 1983; Wada, Clark and Hamm, 1975). Presumably, therefore, structural asymmetry precedes language development and is not the consequence of it. It appears, when comparing different stages of development up through adulthood, that the average hemispheric asymmetry in the Tp area which is present before birth becomes more pronounced with age. Functional asymmetry in children, while not always found, has been observed by Hiscock and Kinsbourne (1982).

Significantly greater than normal reversed asymmetry or lack of asymmetry has also been reported in the brain CT scans of living dyslexic males (Hier, LeMay, Rosenberg and Perlo, 1978). Ten of 24 subjects had a wider right than left parietal-occipital region. Six of the the remaining 14 were symmetrical at that region. They saw no indications of injury using this technique. The ten with reversed asymmetry had lower verbal IQs than the remaining 14 whose left side was either larger or showed no difference. Using the same technique and measurement criteria, Haslam, Dolby, Jones and Rademaker (1981) found that only three of 26 reading disabled boys showed reversed asymmetry; however, the parietal-occipital regions of 11 others were symmetrical. In their sample, there was a relationship between language delay and lack of symmetry.

A somewhat different finding was reported by Parkins, Roberts, Reimarz and Varney (1987). In that study, right handed dyslexics were as asymmetrical as right handed non-dyslexics with respect to the length and width of the frontal and occipital poles. But the occipital poles of left handed dyslexics differed from all (left or right handed) non-dyslexics suggesting that different posterior neuroanatomical organization best describes left handed dyslexic subjects.

Cytoarchitecture of Language Areas

Before it can be assumed that the observed Tp asymmetry has a functional significance in a language disability, it must at least be demonstrated that Tp microstructure parallels its macrostructure. Galaburda, Sanides and Geschwind (1978) have reported a close correspondence between the lateral asymmetry of the cytoarchitectural area which defines Tp and left-right asymmetry observed by gross measurement of the planum in normal individuals. Thus, there is evidence that Tp is structurally contiguous in the normal instance.

In contrast to normal brains, which frequently have sparsely scattered dysplasias in the right frontal lobe (Kaufman and Galaburda, 1989), Galaburda and his colleagues (Galaburda, Sherman, Rosen, Aboitiz and Geschwind, 1985, Galaburda, 1988, Duane, 1989) found bilateral ectopic cell organization in consecutively presenting dyslexic brains which likely occurred prenatally during the second trimester. Similar neural ectopias have been produced in laboratory animals by creating specific lesions *in utero* (Dvorak, Feit and Jurankova, 1978.

Microstrucure asymmetry has also been reported in subcortical structures. Eidelberg and Galaburda (1982) and Ojemann (1977) have found structural laterality in the posterior lateral nucleus (LP) of the thalamus in normal adults and young infants. The projections of this structure to the inferior parietal/angular gyrus area and to inferior frontal speech centers makes this finding particularly interesting. In a single case study, Galaburda and Eidelberg (1982) discovered abnormal micropolygyria in the posterior left temporal lobe and angular gyrus of a dyslexic subject. And, in the LP of the thalamus, they observed bilateral abnormalities in cell bodies and axon myelination. Lesions were also found bilaterally, but left lesions were predominate. A common embryonic origin and migration period (until the end of the second trimester) for the pulvinar-LP complex of the thalamus and its associated cortical targets of projection, the posterior perisylvian neurons, would explain their corresponding abnormalities.

Neural Displacement Model of Dyslexia

Lesion studies in which acquired language abilities have been lost are useful in mapping language functions in the brain. It is known that reorganization may occur following brain insult, but its extent depends mainly on the age of the victim. For example, Kimura (1983) studied 520 patients with unilateral left lesions as a result of stroke and found that when the insult occurred prior to ten years of age there was a left ear/right hemisphere advantage on a verbal dichotic task suggesting that language function was translocated to the right hemisphere. When the insult was later than ten years, the typical right ear/left hemisphere advantage was found; that is, no transfer of language function occurred.

Similarly, Rasmussen and Milner (1977) studied 134 cases of left hemisphere damage occurring before the age of six and 262 cases of later injury. In early injury patients, gross left lesions which spared classical language areas (i.e., where speech is interrupted by electrical stimulation) did not result in translocalization of these areas as demonstrated by pre-surgical amytal test or stimulus mapping during surgery. However, when the lesion encroached upon either frontal or parietal language zones, bilateral representation was more likely to be found, assumed because excision of the damaged left hemisphere was less likely to result in a loss of speech.

But, if there was damage to the posterior temporal region, representation was likely to be relocated posteriorly into the left parietal lobe.

When damage occurred in the older child and adult, Rasmussen and Milner found that left primary language reorganization following a lesion was predominately intrahemispheric. Therefore, they concluded that there is a strong tendency for the left hemisphere to remain dominant for posterior temporal language functions but that displacement, even to the opposite hemisphere, is more common when an injury to language areas occurs before the age of six.

The recruitment of adjacent tissue to serve a lost function has been demonstrated in the young, non-human primate. Glees and Cole, (1950) Cole and Glees (1954) were able to show this following surgical lesions to the sensorimotor strip.

Given this evidence, Geschwind and Galaburda (1985) have proposed that reading disability is the result of anomalous neural development which has its beginnings prenatally. It is well established that briefly induced intrauterine changes can have far-reaching, sometimes tragic, effects on the developing central nervous system. They posit, therefore, that dyslexia has its beginnings in the interaction between the prenatal chemical environment and slowed maturation rate in the language areas, prolonging the vulnerability of the fetal brain and increasing the probability of anomalous neural organization. Genetic factors (such as the makeup of the fetal environment, neural cell sensitivity, or rate of maturation) can also be influential.

Insofar as maturation rate is significantly slowed or tissue is impaired, afferent projections will be deprived of normal competition and, consequently, normal cell death will not occur. Consequently, the projection regions would be larger than is normally seen, as has been shown, for example, by Goldman-Rakic and Rakic (1984) in the non-human primate. Galaburda et al (1985) suggest that this explains their finding of larger right (and therefore more symmetrical) Tp areas in autopsied cases of dyslexia.

The brain stimulation mapping studies of Ojemann (1983) and his colleagues have provided some physiological evidence for displacement of language areas. This methodology has revealed discrete sites in the left hemisphere in the vicinity of the Sylvian fissure which serve specific language functions. However, in subjects undergoing surgery for the excision of epileptogenic tissue, Ojemann and Whitaker (1978) found more variability in the distribution of language functions than would be predicted based on the classical receptive/productive view of language organization. For example, the identification of phonemes was mapped near Broca's area, mouth-face premotor, and also Wernicke's area as well as inferior parietal regions. Unrelated to the extent of epileptogenic tissue was the finding of more posterior representation of language function in subjects with poorer verbal IQ. Ojemann (1983) proposed that an individual with language displaced from Wernicke's area to the left angular gyrus is at a disadvantage to develop verbal skills.

Left Hemisphere Language Function in Normal and Dyslexic Individuals

Behavioral Measures

Of the behavioral tasks supporting left hemisphere language function, dichotic listening tests have been used the most extensively. In normal subjects of all ages, dichotic listening tasks using verbal stimuli have frequently shown a right ear advantage (REA). That is, verbal stimuli presented to the right ear are more accurately identified and/or recalled than those presented to the left ear (see Geffen and Quinn, 1984, for a review). One explanation for the REA is that, given left hemisphere structural organization to process language and superior contralateral auditory projection to cortex, the right ear input is more efficiently relayed and processed than is the left ear information, which must arrive at the left hemisphere via the corpus callosum.

In spite of the evidence in favor of left hemisphere verbal processing, there are contradictory findings. For example, dichotic stimuli do not always produce a clear effect. Hiscock and Stewart (1984) used two types of verbal stimuli, spoken digits and consonant-vowel syllables (CVs). They found that although digits produced a significant REA, directed attention could bias the effect so that when attention was directed to the left ear, a left ear advantage (LEA) could be achieved. However, when CVs were presented dichotically, the REA was seen even when subjects directed attention to the left ear; attending to the right ear served to enhance that advantage. It appears, therefore, that a left hemisphere/REA is not specific to the verbal material per se but to some inherent feature of language material. It further suggests that CV discrimination requires this left hemisphere, feature-specific analysis.

Tallal and her colleagues have also provided evidence that there are acoustic features of verbal, and also of nonverbal, stimuli which are preferentially processed by the left hemisphere. Using a dichotic listening task, Schwartz and Tallal (1980) demonstrated that the REA of normal adults can be manipulated by synthetically extending the rapidly changing acoustic features which begin CV syllables. The formant transition frequencies which enable one to distinguish the stop CVs /ba/, /da/, /ta/, /ka/, /ga/, and /pa/ were lengthened from their normal duration of 40 ms to 80 ms. These phonetic stimuli were correctly identified at either duration; however, the REA was significantly reduced to the extended (80ms) CVs. This outcome suggested that the left hemisphere was recruited to process the rapidly changing features of language which facilitate phonetic discrimination. Schwartz and Tallal concluded that "...a strong REA (taken to reflect superiority of the left hemisphere) is obtained selectively for signals incorporating rapidly changing acoustic spectra, of which speech is a good example" (1980, pp. 1380-1381).

Tallal and Piercy (1973; 1974; 1975) have tested this effect in language impaired children, whom they found could identify CVs as well as normals only when the formant frequencies were extended. They concluded that it is the sequencing of the acoustic components of verbal simuli which is insufficient in these children. However, on a task which calls for repeating rapid sequences of non-verbal auditory stimuli, only 45% of a group of dyslexic boys were significantly impaired (Tallal, 1980), suggesting that fast sequence processing is not the only deficit involved in dyslexia.

Physiological Measures

Evoked Potentials

Auditory evoked potentials (AEPs) to dichotically presented stimuli also suggest left hemisphere involvement in normal language processing. Recording over temporal areas, Van de Vijver, Kok, Bakker and Bouma (1984) presented words dichotically. Right ear dominant subjects had a larger right ear-left hemisphere amplitude; left ear dominant subjects showed no difference and had twice as much variance.

In another AEP study, Wood, Goff and Day (1971) presented two consonant-vowel syllables (CVs) binaurally to subjects who identified one or the other as a target according to instructions. In a separate condition, subjects identified sounds which differed from the CVs by having a formant frequency removed, thus eliminating their phonetic properties. They recorded from T3, T4, C3, and C4 (referenced to linked ears). AERs from the right hemisphere were identical in both tasks but left hemisphere records were significantly more negative to CVs than to the non-word, acoustic stimuli. Like Tallal, they interpreted these findings as reflecting a unilateral left hemisphere mechanism for the processing of the fast frequency linguistic features necessary for speech perception.

ERP studies using simple sensory stimuli have typically not revealed differences between good and poor readers (Sobotka and May, 1977; Weber and Omen, 1977). For example, Yingling et al (1986) when using clicks and flashes, found that no visual or auditory ERP components distinguished reading disabled boys from those of normal reading ability. In spite of these reports, lower amplitude and slower latency ERP components, left hemisphere deficit, and indications of attentional problems are typical electrophysiological findings in reading disabled children (see Sobotowicz and Evans, 1982 for a review).

In a recent visual evoked potential study, Harter, Anllo-Vento, Wood and Marvin-Schroeder (1988) found a longer onset latency of components and also reduced attention-related amplitudes toward a relevant letter stimulus in a group of reading disabled boys. A positive component recorded from the left central area at a latency of 240 ms (presumed to reflect left temporal activity) was found to be of lower amplitude in dyslexic subjects. The dyslexic subjects were able to perform the task just as well as normal subjects; therefore, some of the differences observed were interpreted as reflecting a left central deficit and others as compensatory mechanisms, either behavioral or structural.

Using the same paradigm, a similar result has been found in a group of adult male subjects who were two years or more behind their peers on childhood tests of reading skills (Naylor, 1987). In addition to generally reduced positivity, there was a bilateral, low positivity recorded from central electrodes at 240 ms. Although still subnormal, the greater the amplitude of the P240 component the higher the scores on estimates of adult reading ability in these subjects.

Brain Electrical Activity Mapping (BEAM)

Duffy, Denckla, McAnulty and Holmes (1988) have tested a group of boys who are "pure" dyslexics. That is, reading disabled subjects free of hyperactivity, motor problems, and dyscalculia. They reported that, compared to normals, RD subjects had what they called "aberrant" posterior left hemisphere electrical activity during auditory phonetic discrimination. They also found that aberrant activity was associated with higher scores on verbal tasks, suggesting compensatory activity. These subjects also showed reduced frontal activity which was proposed to reflect attentional impairment in this group.

Positron Emission Tomography

PET scans of normal brains have also indicated a left hemisphere advantage for verbal processing. Bartlett and Brown (1987) found that the unstimulated brain was symmetrically activated but that while identifying target phonemes there was corresponding activity in non-contiguous, mostly left hemisphere regions. The left intrahemispheric correlations were between the classical language areas - Broca's and Wernicke's areas - and also with transverse and infero-frontal cortex and with anterior superior frontal regions thought to reflect attentional processes.

Similarly, Mazziotta, Phelps, Carson and Kuhl (1982) found higher mean metabolism in the left hemisphere and left posterior superior temporal lobe when subjects listened to a prose story as compared to matching tonal strings. And, phonological processing (rhyming) of visually presented stimuli has been shown to engage the left temporo-parietal region (Petersen, Fox, Posner, and Raichle, 1988).

Compared to normal subjects, Gross-Glenn, Duara, Yoshii, Barker, Chang, Apicella, Boothe and Lubs (1986) found more asymmetrical activation during oral reading in the anterior superior temporal cortex of four reading disabled subjects, some of whom had greater activation on the right. The same group (Duara, Gross-Glenn, Barker, Loewenstein, Chang, Apicella, Yoshii, Pascal and Lubs, 1989) have reported localized frontal and inferior occipital differences between normal and dyslexic subjects during a single word reading task.

Regional Cerebral Blood Flow

There have been many rCBF studies showing selective left hemisphere responses to verbal stimuli (Risberg, Halsey, Wills and Wilson, 1975b; Wood, Taylor, Penny and Stump, 1980; Gur, Gur, Obrist, Hungerbuhler, Younkin, Rosen, Skolnick and Reivich, 1982; Maximilian, 1982; Mazziotta, Phelps, Carson and Kuhl, 1982). On a silent reading test, Jacquy, Piraux and Noel (1977) compared ten normally sighted adults, seven blind adult Braille readers, and 17 children between six and ten years old. The children's blood flow was symmetrical. Sighted and blind adults both activated the left precentral and temporal areas. Predictably, sighted subjects had significantly elevated occipital regions while blind subjects did not show significant increases above baseline in the occipital lobe.

Only two rCBF studies using dyslexic adults have been published to date. Both studies found differences between normal and dyslexic subjects, but neither supported a left hemisphere deficit theory of dyslexia. The first (Hynd, Hynd, Sullivan and Kingsbury, 1987) compared two severely reading impaired males with two normal males, recording cerebral metabolism changes as they read a prose story silently. Resting baseline flows were used for comparison to task-related flow values. Normal subjects increased their temporal flow bilaterally while reading, more in the right than in the left. One dyslexic had normal left hemisphere flow, but his right hemisphere flow was lower than that of his normal control. The other disabled reader had overall lower flow in both hemispheres as compared to normal with his right hemisphere activation actually lower during reading than it was at rest.

The second rCBF study, reported by Rumsey, Berman, Denckla, Hamberger, Kruesi and Weinberger (1987), compares a group of 14 reading disabled subjects to 14 normally reading controls on a semantic classification task. Compared to controls, right-handed adult males with a history of reading disability had greater left than right cerebral metabolism during a semantic classification task. There was a non-significant trend toward greater right than left activation as well as significantly less anterior-posterior difference in the RD group when the task was a visual-spatial one. They interpreted their results as a failure to support the proposition of an underactivated left posterior region in reading disabled adults during verbal processing and proposed instead that in the reading impaired adults there is "inadequate bihemispheric integration or inefficient' simultaneous allocation of resources" (page 1149).

Although, neither of these rCBF studies demonstrates a left hemisphere deficit in the dyslexic subjects used, there are several reasons to be cautious about their results. First of all, there is reason to question the use of rest-to-test comparisons, particularly when the sample is too small to allow for statistical control of subject variables such as IQ and anxiety. Prohovnik, Hakansson and Risberg (1980) found high variability in association areas during resting measurements and others have found a sensorimotor control task to be preferable to an uncontrolled rest condition (Stump, Cooke, Yonovitz, Perez and Meyer, 1979; Hannay, Leli, Falgout, Katholi and Halsey, 1983).

Secondly, in the Rumsey et al study, eight or more probes were averaged together. Though the location of the individual probes is not given, it is likely that some are located over or near language processing areas. The possibility exists that combining measurements in this way "swamps" responses from more localized, specific processing areas.

Finally, and importantly, the tasks used may not be appropriate to the issue of a specific deficit in the core language processing regions of the left hemisphere. A silent reading task, while seemingly ideal, is a complex one involving the additive effects of at least visual input, motor activity, and memory (Larsen, Skinhoj and Lassen, 1979; Petersen, Fox, Posner, Mintun and Raichle, 1988) and, in a disabled reader, reading is a comparatively difficult and anxiety-provoking activity. Likewise, a semantic classification task would not necessarily be expected to tap core language skills (Kok and Rooyakkers, 1986; Lang, Lang, Goldenberg, Podreka and Deecke, 1987; Wood and Naylor, 1988). The behavioral studies already reviewed demonstrate the importance of stimulus material for selectively engaging the left hemisphere. A better stimulus choice would be one related to basic language skill acquisition.

Therefore, to investigate the question of a persisting left hemisphere neural deficit in dyslexia, what is required is a task shown to engage left hemisphere language regions, performed by a group of adults of varying reading ability whose early reading histories and overall ability are documented. Such a group was available for the present study. The rCBF technique is considered appropriate for measuring a physiological response in an adult sample, and it also meets the temporal requirements of sustained cognitive activation.

Reliability and Validity of Regional Cerebral Blood Flow

Studies using different physiological techniques to study brain activity in normal and reading disabled individuals have been cited. Each technique has advantages and disadvantages in the study of a neural deficit hypothesis in dyslexia (Wood, 1980, 1083). Event-related potentials have the advantage that any age subject may be used and virtually any scalp locus may be chosen as a recording site. However, brain metabolism techniques offer more precise source localization and also allow sustained tasks.

rCBF reflects neuronal activity indirectly by the coupling between blood flow and local changes in neuronal activity. The precision of coupling has been demonstrated in the sensory system of the laboratory rat (Greenberg, Hand, Sylvestro and Reivich, 1979) and in human subjects

(Raichle, Grubb, Gado, Eichling and Ter-Pogossian, 1976; but see also Raichle and Fox 1986). It is assumed that local changes reflect the sensitivity of contractile proteins in blood vessels to the local pH level of the blood which is, in turn, defined by CO2 concentration (Ingvar, 1979). Local capillary changes are also known to be responsive to neurotransmitters, for instance, excitatory and inhibitory neurons are frequently found together within the vessel endothelium (Pickel, 1986).

Reliability of the rCBF technique has been studied in both resting and activated states. Prohovnik et al (1980) found that there were high correlations among primary sensory projection areas during resting states but that association areas, when not engaged by a task, were not significantly correlated. On repeated measurement, there was a general reduction in overall flow but with a typical hyperfrontality maintained. Risberg, Maximilian and Prohovnik (1977) did repeated rest (with eyes closed) and test rCBF studies (solving Raven's Progressive Matrices) with a group of normal subjects and found that the rest patterns were highly reproducible but that when a test condition was repeated only post-central flows remained the same. The diminution of hyperfrontally over repeated trials of a task has been a frequent finding and may persist over several weeks (Wood, Armentrout, Toole, McHenry and Stump, 1980).

The literature is rich with studies clearly establishing the validity of externally detected blood flow changes as they relate to specific types of cortical activation. For example, motor strip specificity has been demonstrated by Roland, Skinhoj, Larsen and Lassen (1977) who found an increase in flow in the contralateral sensorimotor hand region when a subject maintained static contraction of the forefinger and thumb. Similarly, Melamed and Larsen (1977) measured increased activation between the hand and face areas and in the frontal eye fields during voluntary conjugate eye movements. Lassen, Roland, Larsen, Melamed and Soh (1977) were able to measure flow increases in corresponding contralateral sensorimotor areas by having subjects tactilly discriminate objects with the hand, mouth or foot. Auditory or visual stimulation (Lassen et al, 1977); Melamed and Larsen, 1977) bilaterally activated the auditory and visual cortices, respectively. Larsen et al (1979) found that cortical activation due to speaking, moving the eyes, and hearing independently stimulated the mouth sensory and motor regions, the frontal eye fields, and posterior temporal and occipito-temporal areas but that reading, which combines those behaviors, activated all these regions as well as the supplimentary motor cortex.

Cognitive demands also have been found to selectively activate regions of the cortex. Several studies have reported greater left than right hemisphere blood flow during verbal tasks and the reverse for non-verbal tasks (Risberg, 1980; Gur et al, 1982). Even more complex functions, such as right-left discrimination (Leli, Hannay, Falgout, Wilson, Wills, Katholi and Halsey, 1982) and semantic versus episodic memory (Wood et al, 1980) have yielded unique patterns of flow enhancement. rCBF has also been useful in distinguishing normal brains from such pathological conditions as Alzheimer's disease (Ingvar, 1983), schizophrenia (Gur, Gur, Skolnick, Caroff, Obrist, Resnick and Reivich, 1985; Wood and Flowers, 1988), and affective disorders (Flowers, Wood and Gaby, 1987).

Specific Theoretical Predictions

Evidence from lesion outcome studies, and also from behavioral and physiological studies, generally supports a left hemisphere substrate for verbal skills essential to efficient language processing. Poorer performance by reading disabled subjects on basic tasks like phoneme identification, spelling, and naming, together with the discovery that dyslexic and normal subjects have measurable left hemisphere differences when engaging in language-related tasks, suggests a link between left hemisphere processes and reading. In addition, dyslexic individuals have been shown to have atypical neural formations and unusual cortical organization in the left hemisphere language areas and also to lack the usual larger-left-than-right temporal language asymmetry. Functionally, either from lesion studies occurring early in life in which large areas of the posterior temporal lobe have been involved or from electrical stimulation studies in which language processes have been displaced, the immediately posterior angular gyrus has been implicated in compensatory language processes.

Based on the evidence, it was to predicted that: (1) in a normal, non-clinical population, a language-based task would be accompanied by focal activation of the left hemisphere perisylvian language regions, specifically Broca's and Wernicke's areas; (2) in an adult population which included subjects with documented childhood reading impairment (dyslexia), displacement of activation to surrounding regions, in particular the angular gyrus, would be related statistically to the degree of early disability; and (3) on a task which relies principally on basic, strategy-free language analysis, such as phonetic discrimination, a posterior (angular gyrus) displacement of activation in impaired subjects would be interpreted as evidence of a neural deficit.

A large sample of adults (the Orton group), whose childhood reading and academic histories were fully documented, were compared to normal, adult males in this investigation. The great advantage of using the Orton group was that a diagnosis of dyslexia could be made solely on the basis of childhood reading, which could then be used to predict adult blood flow patterns elicited by cognitive tasks. Thus, regardless of adult accomplishment due to training or practice, a neurophysiological deficiency hypothesis could be tested.

CHAPTER II

METHODS

Two experiments are reported on adult, male subjects. They share the same equipment, stimuli, and procedure but utilize different sets of subjects. For the first experiment, an orthographic analysis task and two verbal memory tasks were performed by a group of 22 normal adult males and another group of 20 subjects from the Orton sample. Only the effects of the orthographic task are reported here.

In the second experiment, an additional 19 normal and 27 referred subjects performed three tasks, the orthographic task, a phonetic discrimination task, and a tone discrimination task.

Subjects

For the first experiment, a normal sample of 22 subjects (ranging in age from 23 to 42) performed an orthographic analysis task. All subjects were of average intelligence which, due to time constraints, was estimated from two verbal (vocabulary and digit span) and two performance (block design and digit symbol) subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981). (Table 1) By self report, all had completed high school without receiving remedial reading instruction or repeating any grades. None wrote with his left hand. Recruitment was by advertisement and subjects were paid for their participation. Procedures and safety factors were explained and informed consent was obtained.

Twenty-nine subjects tested in Experiment 1 were located through the files of June L. Orton who directed the Orton Reading Center in Winston-Salem, North Carolina from 1957 to 1972. The files, maintained at the Health Sciences Library of Columbia University in New York City, contain the records of over 1000 children, many of whom were referred to the reading center for suspected reading disability. Detailed parent and teacher interviews, school reports, and scores on standardized reading, achievement, and IQ tests, were available with the signed consent of participating subjects.

Subjects recruited from the Orton files (ranging in age from 24 to 44), hereafter referred to as the Orton group, were assigned to reading levels on the basis of childhood reading ability using the Boder Reading Quotient (BRQ) according to the formula of Boder and Jarrico (1982):

$$\text{BRQ} = \frac{\text{Reading Age}}{\text{Chronological Age}} \times 100$$

Reading age is defined as the reading grade level, determined by an oral reading test, plus five. Reading had been evaluated by the Gray Oral Reading Test (GORT; Gray, 1955) and the Wide Range Achievement Test (WRAT; Jastak and Bijou, 1945) and was reported in the subject's archival record. If both of the two oral reading quotients (based on the GORT and on the WRAT reading subtest) were 81 or below (n=14), a subject was said to be reading disabled (RD). If both quotients were 92 or better (n=6), then the subject was classified as a non-impaired reader (NI). All others (n=9) were classified as uncertain, and therefore excluded from further analysis. The cut scores of 81 and 92 were chosen to represent local school guidelines for learning disabled classification at the time of our recruitment; that is, the equivalent of 1 1/2 years behind the reading grade level at the beginning of the third grade.

For the Orton group, current reading level was evaluated by the GORT, which yields scores up to the 12th grade level. This score may then be used to calculate the Finucci discrepancy index (FDI), the difference between actual and expected reading level based on verbal IQ and sex (Finucci, Whitehouse, Isaacs and Childs, 1985). All subjects in the Orton group were given a full WAIS-R.

$$\text{FDI} = \frac{\text{GORT} - [(.696 \times \text{Verbal IQ}) + (9.296 \times \text{sex*}) - 9.565]}{8.783}$$

*Male=1

The equation was developed using a stepwise multiple regression procedure with age, sex, education, and verbal and performance IQ as predictor variables of reading ability in a sample of 90 adults with no known dyslexic relatives. The equation was double cross-validated on half-samples of the regression group, and was further validated by showing significant positive ($p<.01$) correlation between the discrepancy score and self-reported reading habits and attitudes. Additionally, when the equation was used to assign scores to a group of 154 family members of RD children, the mean deviation score differed significantly from that of the normal control group.

By interview, all subjects were free of known neurological impairment, major psychopathology, hearing or other sensory impairment, or chronic pulmonary dysfunction.

For the second experiment, nineteen right-handed subjects (ranging in age from 20 to 42) of average IQ were tested. Handedness was assessed by an inventory designed by Briggs and Nebes (1975). Several changes were made in the evaluation of the second normal sample. First, while childhood reading and IQ scores were not available, it was possible to obtain cumulative school records for 17 of the 19 subjects to verify claims that none had repeated a grade and that language grades and verbal scores on standardized group tests were commensurate with overall school performance (that is, there was no indication of a language-specific problem). Second, adult oral reading ability was quantified using the GORT. Third, IQ was estimated using a complete WAIS-R. The GORT and WAIS-R results could, therefore, be used to calculate the FDI. Finally, subjects reported state anxiety before and after the rCBF procedure, using the Speilberger State-Trait Anxiety Index (Spielberger, Gorsuch, Luchene, Vagg and Jacobs, 1983). These two measures were combined to give a single anxiety score. In addition, a self-report rating of task difficulty was administered to each subject. This consisted of indicating on a scale from one to seven, from very easy to very hard, how difficult they perceived each task to be.

Also for the second experiment, 27 additional Orton subjects (ranging in age from 23 to 44) were recruited and evaluated in the same way as previously described, yielding RD (n-11) and NI (n-16) subjects. The self-report measure of task difficulty was also administered to these subjects. (Table 2)

Equipment

A Novo Cerebrograph 32C system (Novo Diagnostic Systems, Bagsvaerd, Denmark) was used to dispense a radioactive tracer (133-Xenon), collect expired air, and measure gamma emissions from the head. A Digital PDP-11 minicomputer gave a continual on-line numeric and graphics display of the technical quality of ongoing measurements. Signals warned of CO2 and O2 abnormalities. Disposable bacteria filters prevented cross-contamination of subject and equipment. An intercom system (a microphone in the subject's face mask) permitted patient-operator communication during measurement periods. A highly sensitive leak detector monitored leakage from the face mask, a soft plastic device fitted over the subject's nose and mouth to collect expired air. The subject was allowed to adapt and breath normally.

For each measurement, a mixture of air and concentrated 133-Xenon (approximately 7 mCi/liter of air) was administered for one minute while clearance was measured by 16 NaI (Tl)-crystal scintillation detectors mounted in shielded lead collimators. Each detector was 3/4" in diameter and 3/4" high; collimators were 20 cm long. The detectors were held in place, eight over each hemisphere, by a lead-lined helmet. Each probe detects radioactivity in a truncated cone of tissue beneath it. At a distance of 2 1/2 mm below the surface of the brain, 50% of the radioactivity is scattered. Therefore, sensitivity of the detectors and scatter of radioactive emissions is such that activity deeper than approximately 30 mm from the surface of the scalp cannot be resolved (e.g., a 30% increase in basal ganglia metabolism cannot be detected - Roland, 1985).

The physical half-life of 133-Xenon is 5.27 days, but the biological half-life is on the order of minutes since the gas is inert and is expired almost immediately in diminishing amounts with each exhalation. The radiation level, which is approximately 25 mCi per study, is well within safe limits even with a large number of repeated doses. The rCBF procedure and this experiment were approved by the Internal Review Board and Committee for Radiation Safety of Bowman Gray School of Medicine where the research was carried out and by the peer review committee and program staff of the funding agency, the National Institute for Child Health and Human Development. The Human Subjects Committee of the University of North Carolina at Greensboro, where the author is a degree candidate, also approved the project.

Values representing blood flow under a given detector are calculated by the clearance rate of tracer material from that area. Specifically, during the first minute isotope mixed with room air is inhaled, rapidly reaching its maximum saturation level. Tissue saturation declines relative to the amount of blood flowing in the tissue under the probe as soon as isotope inhalation ceases (at the end of the first minute). The PDP-11 computer calculates the rate of emission decline beginning when saturation drops 20% from its maximum level and continues over the next minute. Scintillations are averaged in five second bins for each detector. The balance of the 11-minute measurement period serves to calculate corrections for clearance from non-neural tissue (i.e., sinuses, bone, etc.). The value calculated, the Initial Slope Index (ISI; Risberg, Ali, Wilson, Wills and Halsey, 1975a) represents almost entirely gray matter flow since gray matter metabolism during that period is approximately four times that of white matter (Obrist, 1975). This has been shown to be an accurate estimate of the metabolic rate of gray matter under the probe site (Greenberg et al, 1979; Raichle et al, 1976).

Proper head placement in the helmet was assured by matching markers on the helmet to anatomical features. Exact area of measurement is approximate (Figure 1) but was originally verified for this protocol using both X-ray and cadavers and found to be accurate to within .5 cm in those cases (Stump, 1978). There is necessarily some variation since the same helmet is used for all head sizes. An air collar around the helmet prevented any face mask leakage from reaching the head detectors.

Stimuli

For the orthographic task, a Realistic SCR-2500 cassette receiver delivered monaural, single word stimuli through Lanier monaural earphone inserts. The cassette tape, an Ampex AVX 60 Studio Master, was a Dolby recording of 88 common, high imagery nouns (Paivio, Yuille, and

Madigan, 1968) spoken by a female voice. A random half of the 88 words had exactly four letters. The words were delivered at 2 1/2 second intervals, the entire task taking 3 minutes and 40 seconds. Subjects made a bimanual fingerlift response with each forefinger when they heard a word exactly four letters long. Hits and False Alarms were recorded. A preliminary test of the task using non-referred adult male volunteers yielded a hit rate of between 68% and 100% (average d-prime was 5.05).

For the phonetic discrimination task, six stop-consonant syllables (CVs) of 300 ms duration were provided by courtesy of the Neurodevelopmental Center at the University of California, San Diego. They were synthesized on a Bliss system at Brown University and digitized by a Commodore Amiga 2000 computer. CVs (/ba/ /pa/ /ta/ /ka/ /da/ /ga/) contain unique formant frequencies in the initial portion of the consonant which make each one distinctive. The formants were followed by identical bursts representing the short vowel sound /a/. The CVs were partially masked by speech babble (indistinguishable noise containing speech frequencies) to increase the difficulty of the task. One CV (/da/) was designated the target and was randomized with the other five CVs in blocks of 12, repeated 19 times. Subjects were instructed to push a button with the right forefinger after identifying the target CV. A preliminary test of the task yielded an average accuracy rate of 80%.

The tone discrimination task consisted of six pure tonal frequencies (200, 1200, 1300, 1400, 1500, and 1600 hz) synthesized by a Commodore Amiga 2000 computer. These were equal in duration and interstimulus interval to the stimuli used in the phonetic discrimination task, but contained no speech-like characteristics. The 200 hz tone was designated as the target and presented twice in each block of twelve, randomized with two presentation each of the five non-target tones. The blocks were repeated 19 times for a total of 228 stimulus presentations, 38 of which were target tones. Subjects pushed a button with the right forefinger to indicate identification of the target tone.

A pure tone task was chosen because behavioral studies using a similar monaural presentation of high and low tones (Davidoff and Done, 1982) yielded no ear advantage regardless of the frequency of the tone or the ear of entry. In two other studies, response to binaurally presented 1000 Hz tones (Simon, 1967) or response to the onset of pure tones of varying frequency (Emmerlich, 1981) did not differentiate between the ears.

The phonetic and tone tasks took 9 1/2 minutes. Hits, False Alarms, and reaction times were recorded. A response window was set to limit correct responses between

100 msec and 1 1/2 seconds following stimulus presentation. This precaution served to prevent a premature response from being counted and yet allow recovery from one response before presentation of the next stimulus.

Procedure

Following informed consent, the subject was escorted to the rCBF laboratory at Bowman Gray School of Medicine and oriented to the equipment and procedure by an experienced technician. He was then encouraged to ask the technician any questions about the procedure. After filling out the Spielberger State Anxiety Inventory, he lay supine on a padded table with his head positioned in the blood flow helmet and the detectors pushed into place, resting comfortably against the scalp.

Before any task instructions or measurements began, a brief trial was run. This consisted of placing the mask over the nose and mouth so that the subject could experience the pressure of the mask. After a minute of normal breathing with eyes closed, the face mask was removed and the head re-positioned as necessary for the subject's comfort. The purpose of the trial run was to reduce anxiety due to the novel situation and to insure that the subject was comfortable with the procedure.

Prior to the start of each activation task, the face mask was positioned, the subject's eyes closed, and instructions for the task given. For the orthographic task, the stimuli were begun at the same moment that the 133-Xenon gas was delivered. Each measurement period was 11 minutes long and twenty minutes was allowed between tasks. Blood pressure was recorded at the end of each measurement. Order of presentation was randomly counterbalanced.

A practice block of 30 CVs preceded the phonetic and tone tasks. The practice block was repeated if necessary until the subject could perform the task with a hit rate of at least 75% and a false alarm rate of no more than 25%. Both tasks were begun just prior to administration of the tracer. Following the administration of all tasks, the anxiety inventory was completed again.

Choice of a Sensorimotor Task

In this study, the tone task served as a sensorimotor control (SMC) in lieu of the traditional "resting" baseline comparison task. During a resting baseline, subjects merely lie still, usually with the eyes closed. Ears may be plugged or not; lights may be dimmed. The assumption is that the resulting blood flow profile represents an alert, neutral state. However, Prohovnik et al (1980) found that association areas were not highly correlated across repeated baseline studies. In addition, Wood (1980; 1983) has argued the importance of deconfounding comparison tasks by holding the stimulus and response constant and varying task demands. And, in further studies, Leli et al (1982) and Hannay et al (1982) compared an activation task to both resting and SMC conditions, concluding that the resting control comparison demonstrated only generally increased activation while the SMC comparison revealed localized changes of small but significant magnitude which would otherwise have been missed. Finally, Stump et al (1979) compared rCBF during either a resting baseline, SMC (auditory stimulation), or passive listening to words and found that an advantage was gained in that the SMC was significantly less variable than the resting control condition.

The tone task held constant as many of the parameters of the phonetic task as possible (stimulus duration and interval, sensory modality, number of motor responses required) while varying the feature of interest (i.e., verbal versus nonverbal characteristics; Wood, 1980).

CHAPTER III

RESULTS

Experiment 1

Analysis

For the purpose of statistical evaluation, Initial Slope Index (ISI) values for each of the 16 probe sites was converted to a corrected score based on averaged, hemispheric activation according to the following formula: [(ISI-hemispheric mean flow)/hemispheric mean flow] X 100. This correction equalizes the subjects for general arousal level, allowing a comparison of relative regional activation across subjects.

In the forthcoming analyses, two sources of variance, age and IQ, are controlled. Age, which in this study ranged from 24-44 years, has frequently been reported to affect blood flow, increased age being associated with decreased flow (Naritomi, Meyer, Sakai, Yamaguchi and Shaw, 1979). Wechsler fullscale IQ, which ranged from 85-146), was also controlled to assure that predicted differences in flow were not due to differences in general ability. Some reports have shown an effect of IQ on general flow. The Tables, as referenced, show the contributed variance of the linear model (R-square).

Results

Normal Subjects

Task performance. Mean task performance was expressed as d-prime, reflecting both correct responses and correct rejections, independently of response bias toward either misses or false alarms (Green and Swets, 1966). Average d-prime for these 22 male subjects was 4.94 (S.D.=1.11) with a possible perfect score being 6.00, indicating that the target stimulus was readily differentiated from the non-target stimuli.

Regional cerebral blood flow. The rCBF profile (Fig. 2) of Initial Slope Index (ISI) values plotted by sites in the left and right hemispheres showed a general anterior-to-posterior slope typically seen in normal, alert subjects. This so-called "hyperfrontality" is one of the earliest and most frequently reported findings in the rCBF literature (Ingvar, 1979; Risberg, 1986). In this profile, there are peaks of activation superimposed on the overall slope at the prefrontal motor cortex and, as expected for an auditory task (Lassen et al, 1977), at the primary auditory sensory areas of both hemispheres. These same peaks and valleys stand out in sharp contrast when all values are expressed as a percent of the hemispheric mean flow. (Figure 3)

Task accuracy predictions of blood flow. Only left probes 2 and 5 were relevant to the hypothesis of selective left perisylvian activation with higher accuracy of task performance. D-prime positively predicted flow at the left hemisphere premotor area of Broca (probe 2; F=4.88, p=.0403) (Table 3) and at the left posterior superior temporal area of Wernicke (probe 5; F=7.53, p=.0133) (Table 4). In post hoc analyses of all other probes, one additional significant positive relation was found at the right hemisphere premotor region (probe 2; F=7.12, p=.0156).

Orton Subjects

Task performance. Table 1 shows the average age, education, task performance (d-prime), and IQ scores for 20 male subjects recruited from the Orton group. These subjects differed from the normal sample by being older and having more education. The Orton group did not perform the task as well as normal subjects.

Regional cerebral blood flow. In the Orton group, the hyperfrontal pattern was seen only in the left hemisphere, along with a peak elevation at the auditory receptive area and a noticeable elevation at the right angular gyrus. (Figures 4 and 5)

Task accuracy predictions of blood flow. A general linear model, using age and WAIS-R fullscale IQ as controlling variables, tested all probe sites. A significant negative relationship was seen in the left angular gyrus (F=5.34, p=.0345) (Table 5) such that good task performance was associated with less activation in that region.

Childhood reading level predictions of blood flow. A general linear model tested the hypothesis that those subjects who had been reading disabled children would have different localized areas of activation as compared to those who had been good readers. According to the hypothesis, these differences would be predicted for Wernicke's area (probe 5) and at the angular gyrus (probe 6). Just as in the test of a relationship between d-prime and rCBF, age and IQ were controlled. However, in this test of a relationship between childhood reading level and rCBF, Wechsler Intelligence Scale for Children verbal IQ (WISC; Wechsler, 1949) was chosen as the appropriate conservative covariate for this comparison since the specific question was whether childhood reading impairment had an impact that was separable from the impact of childhood verbal ability.

Figure 6 shows mean hemisphere corrected rCBF measurements by probe sites for the two reading levels. Flow at the left angular gyrus (but not at Wernicke's area) was found to be significantly negatively related to reading level (F=5.65, p=.0312) (Table 6). Equating subjects (by statistical covariance) for self-reported anxiety, task order, WISC performance IQ, handedness, or years of education did not alter this relationship. Right angular gyrus flow was tested experimentally and not found to predict either d-prime or childhood reading classification.

Discussion

In this preliminary investigation with the small group of normal males of average IQ, greater spelling task accuracy was associated with greater activation of the left anterior and posterior temporal language regions, confirming the hypothesis that these regions would be engaged during a verbal processing task in proportion to the accuracy of that performance. It was not apparent what aspect of the task evoked this particular response; nevertheless, the results suggested that in normal adult males there is a correspondence between efficient task performance and the selective engagement of these left hemisphere regions.

Unexpectedly, in the same subject sample, activity at the right hemisphere premotor region (homotopic with Broca's area) was also associated with task d-prime. A similar result from an rCBF study has been reported in a normal population when verbal stimuli were presented to the left ear (Maximilian, 1982). It was proposed that this might be due either to a transfer of verbal information from the right to the left hemisphere or to attentional processes. An attentional explanation was also suggested (Cohen, Semple, Gross, Holcomb, Dowling and Nordahl, 1988) to explain a right inferior frontal enhancement of cerebral metabolism as measured by positron emission tomography during an auditory continuous performance task. rCBF values measured during oral, as compared to silent, reading (Larsen, Skinhoj and Lassen, 1979) would suggest that bilateral inferior frontal activity does not reflect subvocalized naming (however, their measurement was a rest-to-test difference and a relationship between activation and task performance was not reported).

In the Orton subject sample, made up of impaired and non-impaired subjects, task accuracy predicted flow levels, not at Wernicke's area, but at the angular gyrus when age and WAIS-R IQ were covaried. That is, the better a subject's performance on the task, the less he engaged the angular gyrus; conversely, the worse the task performance the more the angular gyrus engagement. It is not clear if the impaired readers activate the angular gyrus to do this task, if the non-impaired readers inhibit this area (perhaps while they simultaneously engage Wernicke's area), or if both occur.

Since task performance differed significantly between impaired and non-impaired subjects, it might be expected that childhood reading level would also predict differential cerebral activation. Such was indeed the case: greater angular gyrus activation was associated not only with less efficient performance of the task but also with childhood reading impairment. This may, of course, be stated another way: relatively less activation of the angular gyrus is associated with more efficient (or accurate) performance and is most typical of the non-impaired reading group.

This relationship was no longer present when d-prime was controlled suggesting that, in this sample, the variance in rCBF due to differences in task accuracy is explainable by differences in childhood reading ability.

These findings served to permit formal, <u>a priori</u> hypotheses about the site of rCBF activation in normals and Orton subjects, for test in a full replication in new subjects. In addition, there were several obvious improvements which could be made in this preliminary study. The normal subject group was not formally evaluated with respect to current reading ability and subjects' reports of normal school progress were not verified. Also, IQ in the original sample was based on selected subscales rather than on a full WAIS-R and right hand preference was assumed by observing a subject's handwriting. Finally, subjective anxiety was obtained from only 11 of the 22 subjects, too few to allow an adequate statistical estimation of its effects on task-specific blood flow.

In addition to replication of the letter task effects, the next experiment would test the role of phonetic activation in the observed posterior displacement of left temporal activation. If a similar displacement of rCBF activation were to be found as a consequence of a task more purely phonetic, then a phonetic component of the displaced activation can be assumed. Conversely, if phonetic activation does not displace posteriorly, then the displaced orthographic activation may well be non-phonetic, possibly even non-linguistic.

Experiment 2-A

All subjects in Experiment 2-A (Exp. 2-A) performed the same spelling task (the orthographic discrimination task) used in Experiment 1. These results are reported as Experiment 2-A (Exp.2-A). In addition, these subjects also were given the phonetic identification task and the tone discrimination task, the results of which are described later as Experiment 2-B (Exp.2-B). WAIS-R fullscale IQ ranged from 79 to 138.

The 19 normal, right-handed male subjects of Exp. 2-A differed from those of Exp. 1 only in that they were older and better educated, They differed significantly from a second Orton sample in several ways, including task d-prime and IQ scores. (Table 7)

The second Orton group of 27 subjects was recruited, evaluated, and classified with respect to reading history in the same way as those in Exp. 1. There were no mean differences in any subject variable between the new Orton sample and the original sample, making them suitable for replication. Even though mean values for the Orton subjects from the two experiments did not differ, subjects were more evenly distributed into reading levels in the second group of subjects: RD=11 and NI=16. (Figure 7) As with the Exp. 1 sample, uncertain (BL) subjects were removed and the analyses were performed only on the definitely defined (RD and NI) childhood reading groups.

Analysis

The same dependent measure, mean hemisphere corrected rCBF, was calculated; and the general linear models described in Exp. 1 were performed.

Results

Normal Subjects

Task performance. Mean task performance, expressed as d-prime, was 4.62 (1.06). This was not statistically different from the task performance of the Experiment 1 normal group.

Regional cerebral blood flow. As with the previous normal group, a typical hyperfrontal rCBF profile with bilateral frontal activity was seen. (Figure 7) The peak of activation at primary auditory cortex was less prominant than that of the first group, however.

Task accuracy predictions of blood flow. Each of the three previously implicated sites was separately analyzed by a general linear model using age and WAIS-R fullscale IQ as covariates. In this experiment only the Wernicke's area(probe 5) activity was significantly associated with performance (F=4.56, p=.0496) (Table 9). Thus, it is the only replicable result.

It was possible in this group to examine the contribution to this effect of self-reported anxiety. No change in the relationship was seen when anxiety was covaried. (Table 10)

Orton subjects

Task performance. Mean task accuracy for the 27 male subjects of the second Orton group was 3.85 (S.D. 1.38). This was not significantly different from the former n=20 Orton group (d-prime=3.76, S.D. 1.23). However, Exp. 2-A reading impaired subjects had significantly lower d-prime scores than non-impaired subjects (t=4.23, .0005).

Task accuracy predictions of blood flow. A general linear model, with variance due to age and WAIS-R IQ controlled, yielded a positive prediction of Wernicke's area activation by task accuracy (F=7.06, p=.0141) (Table 11). Angular gyrus flow marginally, negatively predicted task d-prime (F=4.10, p=.0545); however, it replicated the previous finding. (Table 12) (Figure 8)

Childhood reading level predictions of blood flow. A general linear model tested the prediction of rCBF at the angular gyrus as a function of childhood reading ability. (Figure 9) Blood flow at the angular gyrus of the left hemisphere was found to be negatively predicted by childhood reading classification (F=13.66, p=.0013) (Table 14).

Controlling for either, education, self-reported anxiety, task order, or handedness did not change this relationship. The addition of d-prime as a controlling variable, however, reduced the probability that reading classification could predict activation at the angular gyrus (F=6.04, p=.0185). And the addition of childhood performance IQ also reduced the confidence level (to p=.0575).

Discussion

The new normal sample confirms the Exp. 1 finding of a significant positive association between spelling task performance and activation in Wernicke's area. In contrast to the first normal sample, however, activation related to the task was unique to that site. The Wernicke's area result is, therefore, the replicable and interpretable finding. Thus, in a group of adult males of normal IQ and reading ability, some aspect of this verbal task activates the posterior superior temporal language region of the left hemisphere in proportion to the accuracy of task performance.

The positive association between spelling task accuracy and blood flow in a left hemisphere language area was also confirmed in the Orton group of adults of known and varied reading histories, providing further corroboration that efficient performance of the spelling task is subserved by the classical left hemisphere posterior language region of Wernicke.

The negative prediction of angular gyrus activity by childhood reading classification, seen in the first sample, was also replicated in the second sample of Orton subjects. In Exp. 1, although a positive relationship was also predicted at Wernicke's area, none was observed. However, in Experiment 2-A, Wernicke's area flow was found to be positively correlated with reading ability. Task accuracy and reading classification shared the variance in activation at Wernicke's area; but at the angular gyrus, while some flow variance was found to be due to task accuracy, independent variance was related to differences in childhood reading. Thus, among subjects who differed widely on measures of childhood reading ability, activation of this adjacent region, posterior to Wernicke's area, reflects not only a present inefficiency in task performance, but also (and separately) a childhood deficit.

Experiment 2-B

The findings of Exp. 2-A, of differential cortical activation by dyslexic and good readers during a spelling task, could be explained by a neural deficit in the left hemisphere posterior superior temporal lobe, as has been proposed. Alternatively, observed differences could be due to the engagement by impaired readers of a compensatory mechanism involving the angular gyrus.

As a further test of this issue, a phonetic discrimination task was used. Phonemes, the sound segments from which words are built, have language properties but, although they can be named, do not themselves name anything, nor do they have intrinsic meaning or imageability, allowing for little in the way of strategy choice. The processing of initial fast frequencies which distinguish among one category of phonemes, stop consonants, has been suggested as fundamentally deficient in at least some dyslexic children and in adults with left hemisphere damage. The belief is now widely held that deficits in the basic aspects of phonological processing are responsible for the failure to develop and use written language (Catts, 1989). Further, brain stimulation mapping has implicated the left temporal cortex in phonetic processing. Likewise, auditory evoked potentials, brain electrical activity mapping, and PET studies have all shown that temporo-parietal areas are active during phonetic discrimination tasks (See again Wood et al, 1971; Schwartz and Tallal, 1980; Hiscock and Stewart, 1984; Duffy et al, 1988; Petersen et al, 1988).

In Exp. 2-B, it was assumed that, like the spelling task, a phonetic discrimination task would activate left hemisphere Wernicke's area language processes. But in contrast to the spelling task, the relatively strategy-free phonetic task would more directly test core language processors, reflecting differences in language processing substrate rather than differences in strategy. Therefore, if the posterior displacement by dyslexic subjects seen in the spelling task also were to be seen in the phonetic task, then it would be interpreted as evidence of a true neural deficit in poor readers. Conversely, if no posterior displacement were to take place in the phonetic task, it would be interpreted as evidence that a strategy choice shift could explain the spelling task findings.

Analysis

The dependent measure was a simple arithmetic difference between ISI values for the phonetic and the tone tasks as recorded at the posterior superior temporal and angular gyrus regions of each hemisphere. A general linear model was used to evaluate the relationship between this value and childhood reading level (based on Boder Reading Quotients and classified as previously described in Experiment 1) with variance due to IQ (as given by the appropriate Wechsler test) and age (at the time of rCBF measurement) controlled. This allowed for a direct test of the variance which predicts differences between the two tasks. A significant relationship was predicted only in the left hemisphere at Wernicke's area and the angular gyrus.

Results

Normal Subjects

Task performance. Mean syllable task performance, expressed as d-prime, was 3.97 (S.D. 1.43) and for the tone task was 5.85 (S.D. 0.46).

Regional cerebral blood flow. The rCBF profile of Initial Slope Index (ISI) values plotted by probe sites in the left and right hemispheres for the phonetic and tone tasks are shown in Figure 10.

For both tasks, typical hyperfrontal flow was seen. There was a peak at left Wernicke's area in the control task. Neither mean flow nor ISI values differed across the hemispheres for either task.

A plot of the simple difference between ISI values at a given probe site across tasks is show in Figure 14. A positive value indicates that phonetic task flow was greater than tone task flow at that location. (Figure 11)

Task accuracy predictions of blood flow. Each site was separately analyzed by a general linear model. With the covariates age and WAIS-R IQ included, as was done with the spelling task analyses, no F value was greater than 3.67 and no p value less than .0777.

Orton Subjects

Task performance. Mean phonetic task performance, expressed as d-prime, was 4.13 (S.D. 1.44). Tone task d-prime was 5.56 (S.D. 0.64). These mean performance scores and standard deviations did not differ statistically from those of the n=17 normal group.

Regional cerebral blood flow. The rCBF profiles of ISI values plotted by probe sites in the left and right hemisphere for the phonetic and tone tasks are shown in Figure 12 Visually, much like the profiles for the spelling task, the typical hyperfrontal pattern with a peak at Wernicke's area was seen in the left hemisphere for both tasks.

Task accuracy predictions of blood flow. A general linear model tested the d-prime prediction of the dependent measure (phonetic-tone values) at each probe site. No F value was greater than 1.74 and no p value less than .1988 when age and WAIS-R IQ were controlled.

Childhood reading level predictions of blood flow. The same general linear model tested the prediction of rCBF at Wernicke's area and the angular gyrus as a function of childhood reading classification with age and childhood verbal IQ covaried. (Figure 13) There were no significant relationships.

Discussion

A focal region of activation associated with phonetic processing was predicted to be found at Wernicke's area. It was presumed that this relatively strategy-free task would not allow for compensatory mechanisms, forcing good and poor readers alike to engage the same cortical area, thereby revealing a posterior temporal neural deficit in dyslexia if one existed. The results did not confirm the predictions. Neither Wernicke's area nor the angular gyrus was significantly engaged during phonetic discrimination, as predicted by phonetic or tone task d-prime, in either group of subjects. Also contrary to expectation, a difference in flow across reading levels at either Wernicke's area or the angular gyrus was not seen. This might in part be explained, at least in the phonetic task, by the fact that task d-prime did not differ across reading classifications.

To test whether either phonetic or tone discrimination could account for the variance in left hemisphere responses to the spelling task, each task was separately added to the linear model for prediction of spelling task-induced angular gyrus activation from reading level. No significant variance was thus explained. This finding suggests that those aspects of the spelling task blood flow profile, which are predicted from task accuracy or childhood reading level, are neither phonetic nor simply acoustic (tonal).

Study from Experiments 1 and 2-A

Three findings of Experiment 1 were found to replicate in Experiment 2-A. First, it was demonstrated that a verbal task activates the left Wernicke's area in normal, adult males. Second, with age and adult IQ controlled, activation of the angular gyrus was found to be negatively related to spelling task accuracy in both Orton groups. Third, there was a negative relationship between reading ability and angular gyrus activity in both Orton groups, at least some of which could be explained by the task accuracy measure.

Inasmuch as the normal and Orton subject samples in both experiments appeared to be similar in important ways, they were combined to allow a more complete description of the contributions of other sources of variance. Those results are reported as a Study, based on findings from Exp. 1 and 2-A.

Joining the normal samples resulted in 41 subjects. The Orton group became n=47, with 25 RD and 22 NI subjects. Group means between normal and Orton subjects differed significantly in mean IQ, d-prime, handedness, and adult reading attainment.

Results

rCBF and task accuracy in forty-one normal subjects

The rCBF profile for the combined normal sample is shown in Figure 14. Using the same linear model as for Exp. 1 and 2-A (i.e., age and WAIS-R IQ controlled), regional flow at Wernicke's area was positively predicted by d-prime (F=10.40, p=.0026) (Table 15). The addition of self-reported anxiety level as a covariate (making four variables) yielded a similar outcome for the 30 subjects who had this measure.

rCBF and task accuracy in forty-seven Orton subjects

The rCBF profile for the combined Orton sample is shown in Figure 15. Higher d-prime predicted greater Wernicke's flow (F=7.46, p=.0091) (Table 16), and controlling for anxiety accounted for some variance but did not change the direction of that prediction (F=4.40, p=.0426) (Table 17).

In this combined group, angular gyrus activity, using the same age and IQ controls, was also predicted by d-prime (F=8.89, p=.0047) (Table 18), but the relationship was in the opposite direction from the effect at Wernicke's area. That is, task-related activity at the angular gyrus was negatively correlated with task accuracy. (Again, anxiety as a covariate did not change the finding; F=8.71, p=.0053.) (Table 19)

Childhood reading level predictions of rCBF

The rCBF profile of hemispheric mean corrected ISI values is plotted by childhood reading levels in Figure 16. Analysis of childhood reading predictions of Wernicke's and angular gyrus activation was based on 44 Orton subjects (three did not have childhood verbal scores reported in the archival record). As was previously seen in each Orton group separately, angular gyrus activation was negatively related to childhood reading classification (F=13.42, p=.0007). (Table 20) Verbal IQ contributed positively and independently to activation seen at the angular gyrus (F=4.17, p=.0477).

Equating subjects for d-prime did not account for reading level predictions of angular gyrus activity (F=7.14, p=.0110). That is, significant differences were seen in the angular gyrus across reading levels which could not be accounted for by task performance. Variance due to adult reading outcome (FDI) was then controlled along with age and childhood verbal IQ with the result that angular gyrus activity was shown still to be inversely associated with reading level (F=8.67, p=.0054). (Table 21) In addition, in this extended model, higher childhood verbal IQ remained an independent, positive predictor of greater flow at that location (F=4.46, p=.0412).

Analysis of variance of group and hemispheric differences

Two levels of group (normal and Orton) and two hemispheres (left and right) were analyzed using an analysis of variance. The results yielded a group by hemisphere interaction at probe site 2 (F=14.32, p=.0002) such that, by post hoc comparisons, normal subjects had a more active right probe 2 as compared to Orton subjects, and Orton subjects had lower right than left hemisphere flow. There was a main effect for group at probe site 6, Orton subjects having the greater bilateral activity (F=19.55, p=.0001).

Discussion

Combining subjects who shared the spelling task gave results similar to those seen in the groups separately. In addition, when sufficient sample sizes are used and extraneous variance is controlled, better task performance is shown to predict greater Wernicke's area activation in the Orton group just as it did in the normal group.

Further, the relationship between activity at the angular gyrus and childhood reading classification has been shown to be sensitive both to childhood verbal IQ and to task performance. Importantly, the effect seen is independent of adult reading attainment. That is, the differences found to be related to angular gyrus activity are accounted for by childhood and not adult reading ability.

The question persists: is the difference in angular gyrus activation across two reading levels (RD and NI) due to differential activation by good readers, poor readers, or both? A univariate test yielded a task by reading classification interaction (F=6.02, p=.0090) for probe 5 relative to probe 6. The difference measures, probe 5-probe 6, were found to differ between the spelling and phonetic tasks for NI but not for RD subjects (F=11.34, p=.0021). And NI subjects had a greater slope difference as compared to RD subjects only for the spelling task (F=4.76, p=.0388).

This finding suggests that, when task performance differentiates subjects by childhood reading ability, it is the non-impaired group which can selectively enhance or inhibit relevant language regions, while the impaired group responds similarly to different verbal tasks. This in turn suggests that RD subjects have less ability to allocate the cortical resources best suited to a task while NI subjects can do this with a significant advantage in accuracy.

Large differences between Orton and normal subjects involving right hemisphere activation were seen, but these could not be accounted for by accuracy of task performance or reading classification.

CHAPTER IV

CONCLUDING DISCUSSION

Observations converging from different methodologies have provided evidence for left temporal lobe mediation of some essential features of language. In this investigation using the regional cerebral blood flow technique, normal adults showed the predicted activation of a left hemisphere region which corresponds to the classical language area of Wernicke. This result from a total of 41 neurologically healthy subjects provided support for the left superior posterior temporal mediation of a verbal task. The finding was then confirmed in a second, more varied group of 47 adults which included some severely impaired readers. An additional finding, in the second group, was that the activation of the angular gyrus was inversely related to task accuracy, suggesting that in this more varied sample the posterior region of the left hemisphere also is involved in the processing of this spelling task. Furthermore, angular gyrus activation was also inversely related to childhood reading ability.

This shift of function-dependent activation from Wernicke's area to the adjacent posterior language area by subjects with less reading ability would seem to be consistent with Ojemann's finding that poorer verbal ability is associated with a more posterior neural substrate for language processing. It would likewise be consistent with Rasmussen and Milner's report, also based on brain stimulation mapping, that early left hemisphere lesions involving the temporal language area predispose other nearby (probably parietal) regions of the left hemisphere to assume language functions.

The precise reason for this negative relationship between childhood reading classification and rCBF measured at the angular gyrus is not known, however. The explanation could be purely functional. For example, the difference could be related to perceived difficulty in doing the task. In fact, subject ratings of spelling task difficulty were correlated with spelling task accuracy ($r=.59$, $p<.0001$). However, the relationship between reading impairment and the activation of the angular gyrus did not change when subjects were equated for task performance. Therefore, this seems an insufficient explanation for the apparent enhancement of the angular gyrus observed in the impaired group.

Alternatively, it could be that reading disabled subjects do not activate the region best equipped to process the task efficiently so that a nearby region, also involved in verbal processing but less well equipped to respond to the demands of a verbal task, assumes that function. Possibly, doing the task well requires the concomitant activation of Wernicke's area and inhibition of the angular gyrus, a function best accomplished by non-impaired readers. This functional distinction could be explained by differences in strategy adopted by the good and poor reading groups.

However, the cortical correlates of various strategies have not yet been described. This issue was partly addressed here by asking some subjects to perform a phonetic analysis task, believed to be more strategy free than the spelling task and yet to involvebasic language elements. This task, controlled by a tone discrimination task, was expected to statistically partial out differences due exclusively to strategy versus those due only to a neural deficit. However, the phonetic-tone combination failed to demonstrate either task-related or reading class-related blood flow differences, suggesting that during phonetic analysis dyslexics and normal readers do not differ. Thus, if the rCBF measures appropriately reflect phonetic processing, and if doing this phonetic task requires the same processes as those tapped by Tallal's phonetic discrimination tasks, this finding may challenge the proposal that reading disorders have as their basis the impairment of a phonetic analyzer.

These tasks also served another purpose. When variance in angular gyrus flow as measured during the spelling task was statistically controlled for flow measured during either the phonetic or the tone task alone, the negative reading level/rCBF relationship was still present. This suggests that the neural mechanism which, during the spelling task, distinguishes subjects by childhood reading ability does not reflect either purely phonetic or simple acoustic processing. Therefore, the argument is strengthened that childhood dyslexic and normal readers differentially approach these whole-word stimuli.

However, a strategy explanation also seems an insufficient explanation for group differences since it merely begs the question of why dyslexic individuals as a group would chose a different strategy to do this task. A lesion hypothesis is proposed, therefore, since a logical explanation is that the use of a different strategy would be imposed by a neural insufficiency. That is, reading disabled subjects may activate the same neural structures as non-impaired subjects not because of a choice of strategies but because Wernicke's area, the more efficient neural substrate for the task, is impaired.

Thus, rather than by different strategies, the angular gyrus results could be explained by an altered neural structure hypothesis in RD subjects. That is, the cortical lesions experienced during fetal development presumed to be present in dyslexic individuals could precipitate an atypical pattern of connectivity, with axons which normally are targeted for Wernicke's region finding targets within the angular gyrus.

An example of such altered structural development has emerged in the animal neural developmental literature. Experiments with neonatal hamsters and ferrets provide a model for altered neural structure under lesion conditions similar to those described from the autopsy material of dyslexic individuals by Galaburda and his colleagues. The cortical organization of these animals at birth approximates that of the human fetus toward the end of the second trimester, when a wave of cell migration destined for the superficial cortical layers is in progress. In these studies, it was found that ablating visual target areas and eliminating auditory or somatosensory afferents to their respective target areas results in stable, though not entirely normal, visually-driven synaptic contacts at the unoccupied auditory or somatosensory targets (Frost, 1988; Sur, Garraghty and Roe, 1988).

In dyslexics, a similar re-routing of embryonic axons originally targeted for Wernicke's area but instead terminating on the angular gyrus would constitute a true structural displacement to the posterior adjacent region, established prenatally and remaining fixed. So formed, these atypical circuits perhaps would not be as efficient as those established under non-lesion conditions and would explain why fully normal functions would not develop.

Further support that language functions are assumed by intact tissue as the result of a lesion has support in the neuropsychological literature on infant and pre-school children who have sustained lesions. For example, the work of Rasmussen and Milner and of Kimura, already discussed, is evidence for this. In addition, early childhood left hemispherectomy patients acquire nearly normal left hemisphere language functions in the right hemisphere (Dennis and Whitaker, 1976). However, right hemisphere structures usually fail to acquire this level of language competency after left hemisphere damage in adulthood. That suggests a developmental component to the process of compensation.

Even though the angular gyrus may become "hard wired" during early neural development to substitute for Wernicke's area processes, possibly other more plastic regions of brain are able to compensate for poor childhood reading skills as the result of later experience. This could be why approximately half of the Orton group who were impaired as children were normal readers when evaluated as adults. That is, even though there is no correlation between the finally achieved reading level and angular gyrus activation patterns resulting from the spelling task, perhaps subsequent life events can still modify other neural circuits which come to subserve the development of reading skills.

A relevant animal model for the assumption of relatively normal behavior in spite of a lesion is reported by Glass who demonstrated that in cats monocularly deprived by lid suture (1973), and also in humans with congenital monocular cataracts (1977), visual evoked potentials recorded over primary visual cortex are permanently altered. Evoked responses from motor cortex are altered as well. However, normal visual evoked responses emerge at the motor cortex when the sutured eye is opened and the animal is forced to use the "unexperienced" eye to perform certain tasks. Thus, the initially observed electrophysiological aberrations in the motor area (which receives extrastriate projections) and their subsequent recovery are found, in the cat, to be related to the animal's behavioral interactions with the environment.

Therefore, it might be expected that experience with reading, which occurs between childhood measures of disability and adult accomplishment, promotes remote neural compensation for a permanent Wernicke's area loss. Further investigation may reveal the region subserving such compensation (for example, right hemisphere structures are suggested by Dennis and Whitaker, already mentioned, and by Bradshaw, 1980). It is also possible that a compensation will be reflected in global rather than regional activation.

There are, of course, other explanations for the partial remediation of a disability over time. First, poor early reading may be due to a developmental lag which disappears with maturity. Second, there could be a confounding condition, such as Attention Deficit Disorder, which improves spontaneously, resulting in better performance. Alternatively, it is possible that what was an apparent disability was the result of error either in the testing tools used or in the clinical diagnosis of dyslexia. However, the present evidence that a subject's childhood reading deficits predict adult rCBF measures, regardless of the eventual reading skill attained, argues against any of these explanations. This is more compelling since other subject differences in childhood, such as verbal and performance IQ, have been statistically controlled. Similarly, variables related to either experience (cumulative education) or current state when the rCBF measure was made (self-report anxiety) fail to explain reading level differences in angular gyrus activity.

Furthermore, while current task performance itself accounts for some differences in blood flow, additional variance is still due only to childhood reading ability. This may be interpreted to mean that the angular gyrus activity observed during the spelling task reflects processes which are basic to the acquisition of reading but distinct from those which maintain reading in the adult. And conversely, this line of reasoning further implies that processes related to reading acquisition are not fully reflected in the ability to perform the task accurately and, in fact, could be non-verbal. Insofar as spelling task performance reflects skills underlying reading acquisition, the act of reading by the experienced adult may tap processes other than those necessary in the acquisition stage.

In summary, rCBF activation patterns which result from a spelling task suggest that good and poor childhood readers differentially activate the left hemisphere when doing a verbal task which has been shown to involve left hemisphere language processes. This could be explained by an embryonic Wernicke's area lesion which promotes anomalous cortical connectivity during prenatal development, by the recruitment of the angular gyrus when Wernicke's area is impaired, or a Wernicke's deficit may prevent the inhibition of angular gyrus activation by reading disabled subjects. Since these results were predicted from childhood reading ability and could not be accounted for by available adult measures (adult reading ability, educational experience, or task difficulty), this provides evidence that neural mechanisms subserving normal reading acquisition are fixed relatively early in life.

The mechanism seems neither phonetic nor purely tonal. Inasmuch as some impaired children eventually acquire normal reading ability, other regions will likely be found to be related to compensatory processes.

The variance in rCBF measurements reported here is not completely accounted for by the present categories of childhood reading ability and controlling variables. However, it is not for their ability to diagnose reading disability that these findings are valuable. Rather, their importance lies in what they contribute to an understanding of the development of neural structure which underlies reading acquisition and reading failure, and in the eventual identification of markers which will make early diagnosis and intervention possible.

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APPENDIX A

TABLES 1-20

Table 1

Means and Standard Deviations for Behavioral Measures for Normal and Orton Subjects From Experiment 1.

VARIABLE	Normals (n=22)	Ortons (n=20)
[a]Age	28.2 (6.03)	33.9 (5.33)
[a]Education	14.8 (1.50)	16.1 (2.54)
[a]Task accuracy (d prime)	4.94 (1.10)	3.76 (1.23)
Adult Intelligence Tests*		
Full Scale IQ	112.0 (15.31)	103.9 (11.97)
Verbal IQ	113.6 (16.97)	105.0 (12.55)
Performance IQ	106.6 (10.62)	102.5 (12.33)
Childhood Intelligence Tests**		
Full Scale IQ		109.9 (9.63)
Verbal Scale IQ		108.4 (14.03)
Performance IQ		109.6 (7.80)
Handedness		16.8 (8.53)
Adult Reading Discrepancy***		-1.17 (1.95)

[a] Significant group differences by t-test, $p<.05$

*Based on the Wechsler Adult Intelligence test. For normal subjects, IQ scores are extrapolated from two verbal subscales (vocabulary and digit span) and two performance subscales (block design and digit symbol).

**Based on Wechsler Intelligence Scale for Children.

***Based on the Finucci Discrepancy Index (see text).

Table 2

Means and Standard Deviations of Behavioral Measures for Orton Reading Disabled (RD) and Non-Impaired (NI) Subjects in Experiment 1.

VARIABLE	RD n=14		NI n=6	
Age	34.1	(5.72)	33.5	(4.77)
[a]Educ	15.4	(2.59)	18.0	(1.09)
[a]Task d prime	3.23	(0.78)	5.00	(1.24)
Adult Intelligence Tests*				
Full Scale IQ	101.4	(12.33)	110.0	(9.30)
[a]Verbal IQ	100.9	(12.03)	114.4	(8.24)
Performance IQ	102.2	(12.74)	103.3	(12.44)
Child Intelligence tests**				
[a]Full Scale IQ	106.8	(9.89)	117.0	(3.22)
[a]Verbal IQ	103.7	(13.78)	118.5	(8.57)
Performance IQ	108.5	(8.78)	112.0	(4.94)
Hand	15.6	(9.67)	19.5	(4.55)
[a]Adult Reading Discrepancy***	-1.97	(1.56)	0.69	(1.45)

[a]Significant between group differences by t-test, $p<.05$.
*Based on the Wechsler Adult Intelligence Scale-Revised.
**Based on the Wechsler Intelligence Scale for Children.
***Based on the Finucci Discrepancy Index (see test).

Table 3

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Broca's Area Activation (Probe 5) Predicted from Task D-Prime for n=22 Normal Subjects During a Spelling Task (Experiment 1).

	df	F Value	P Value	R-Square
Model	3,18	2.12	.1332	.261
Sources of Variance				
Task d-prime	1	4.88	.0403	
Age	1	2.01	.1735	
Full Scale IQ*	1	0.00	.9844	

*Based on Wechsler Adult Intelligence Scale-Revised (see text).

Table 4

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=22 Normal Subjects During a Spelling Task (Experiment 1).

	df	F Value	P Value	R-Square
Model	3,18	2.81	.0690	.319
Sources of Variance				
Task d-prime	1	7.53	.0133	
Age	1	1.59	.2228	
Full Scale IQ*	1	0.49	.4923	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 5

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Task D-Prime For n=20 Orton Subjects During a Spelling Task (Experiment 1).

	df	F Value	P Value	R-Square
Model	3,16	2.52	.0950	.321
Sources of Variance				
Task d-prime	1	5.34	.0345	
Age	1	1.95	.1818	
Full Scale IQ*	1	2.38	.1428	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 6

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Childhood Reading Level for n=20 Orton Subjects During a Spelling Task (Experiment 1).

	df	F Value	P Value	R-Square
Model	3,15	1.97	.1615	.283
Sources of Variance				
Reading Level	1	5.65	.0312	
Age	1	1.90	.1877	
Verbal Scale IQ*	1	2.64	.1249	

*Based on Boder Reading Quotient (see text).
**Based on Wechsler Intelligence Scale for Children.

Table 7

Means and Standard Deviations of Behavioral Measures for Normal (NL) and Orton (Ort) Subjects in Experiment 2-A.

	NL n=19		Ort n=27	
Age	32.3	(5.89)	31.7	(5.28)
Educ	16.5	(2.53)	15.8	(2.92)
[a]Task d prime	4.62	(1.06)	3.85	(1.38)
Anxiety	56.5	(11.9)	59.9	(12.02)
Adult Intelligence Tests*				
[a] Full Scale IQ	108.9	(8.92)	101.8	(13.9)
Verbal IQ	109.4	(9.22)	101.9	(14.21)
Performance IQ	106.7	(8.66)	101.9	(13.1)
Phonetic d-prime	3.97	(1.43)	4.38	(1.33)
[a]Tone d-prime	5.85	(.46)	5.47	(.69)
Phonetic Reaction Time	0.63	(.12)	0.62	(.10)
[a]Hand	20.5	(3.91)	13.2	(12.8)
[a]Adult Reading Discrepancy**	.77	(.88)	-0.29	(1.81)
Spelling Task Difficulty***	2.82	(1.13)	3.29	(1.10)

[a] Significant between group differences by t-test, $p < .05$.
*Based on the Wechsler Adult Intelligence Scale-Revised.
**Based on the Finucci Discrepancy Index (see text).
***Based on a self-report difficulty scale.

Table 8

Means and Standard Deviations of Behavioral Measures for Reading Disabled (RD) and Non-impaired (NI) Orton Subjects in Experiment 2-A.

VARIABLE	RD n=11		NI n=16	
Age	32.3	(5.03)	31.3	(5.57)
[a]Educ	14.3	(3.69)	16.9	(1.67)
[a]Task d prime	2.77	(1.20)	4.59	(0.94)
Anxiety	61.2	(12.9)	59.1	(11.81)
Adult Intelligence Tests*				
[a]Full Scale IQ	93.3	(6.72)	107.8	(14.77)
[a]Verbal IQ	91.5	(5.18)	109.1	(14.10)
Performance IQ	98.0	(11.1)	104.6	(13.99)
Childhood Intelligence Tests**				
[a]Full Scale IQ	97.7	(6.86)	117.5	(9.0)
[a]Verbal IQ	95.3	(6.75)	119.5	(9.8)
[a]Performance IQ	102.0	(11.15)	113.9	(8.92)
Hand	13.1	(13.98)	13.25	(12.4)
[a]Adult Reading Discrepancy***	-1.55	(2.02)	0.57	(1.0)
[a]Spelling Task Difficulty****	3.70	(1.25)	2.91	(.83)

[a]Significant between group differences by t-test, $p<.05$.
*Based on the Wechsler Adult Intelligence Scale-Revised.
**Based on the Wechsler Intelligence Scale for Children.
***Based on the Finucci Discrepancy Index (see text).
****Based on a self-report difficulty scale.

Table 9

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=19 Normal Subjects During a Spelling Task (Experiment 2-A).

	df	F Value	P Value	R-Square
Model	3,15	3.06	.0606	.380
Sources of Variance				
Task d-prime	1	4.56	.0496	
Age	1	1.53	.2347	
Full Scale IQ*	1	5.79	.0294	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 10

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=19 Normal Subjects During a Spelling Task (Experiment 2-A).

	df	F Value	P Value	R-Square
Model	4,14	2.39	.1008	.405
Sources of Variance				
Task d-prime	1	5.02	.0417	
Age	1	1.03	.3274	
Full Scale IQ*	1	4.82	.0455	
Anxiety	1	0.61	.4493	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 11

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=27 Orton Subjects During a Spelling Task (Experiment 2-A).

	df	F Value	P Value	R-Square
Model	3.23	2.45	.0896	.242
Sources of Variance				
Task d-prime	1	7.06	.0141	
Age	1	0.95	.3392	
Full Scale IQ*	1	2.08	.1623	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 12

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Task D-Prime For n=27 Orton Subjects During a Spelling Task (Experiment 2-A).

	df	F Value	P Value	R-Square
Model	3,23	1.39	.2718	.153
Sources of Variance				
Task d-prime	1	4.10	.0545	
Age	1	0.21	.6537	
Full Scale IQ*	1	1.48	.2357	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 13

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Childhood Reading Level for n=27 Orton Subjects During a Spelling Task (Experiment 2-A).

	df	F Value	P Value	R-Square
Model	3,21	4.83	.0103	.409
Sources of Variance				
Reading Level	1	13.66	.0013	
Age	1	0.67	.4209	
Verbal Scale IQ*	1	6.81	.0163	

*Based on Boder Reading Quotient (see text).
**Based on Wechsler Intelligence Scale for Children.

Table 14

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=41 Normal Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	3,37	3.68	.0204	.230
Sources of Variance				
Task d-prime	1	10.40	.0026	
Age	1	0.21	.6463	
Full Scale IQ*	1	2.73	.1068	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 15

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=47 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	3,43	2.66	.0604	.156
Sources of Variance				
Task d-prime	1	7.46	.0091	
Age	1	0.68	.4133	
Full Scale IQ*	1	0.96	.3314	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 16

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 5 (Wernicke's Area) from Task D-Prime For n=44 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	4,39	2.22	.0849	.185
Sources of Variance				
Task d-prime	1	4.40	.0426	
Age	1	1.08	.3057	
Full Scale IQ*	1	0.02	.8911	
Anxiety	1	2.22	.1446	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 17

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Task D-Prime For n=47 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	3,43	3.07	.0377	.176
Sources of Variance				
Task d-prime	1	8.89	.0047	
Age	1	0.16	.6949	
Full Scale IQ*	1	2.86	.0981	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 18

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Task D-Prime For n=44 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	4,39	2.21	.0861	.185
Sources of Variance				
Task d-prime	1	8.71	.0053	
Age	1	0.15	.7027	
Full Scale IQ*	1	0.12	.7324	
Anxiety	1	0.12	.7324	

*Based on Wechsler Adult Intelligence Scale-Revised

Table 19

Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Childhood Reading Level for n=47 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	3,40	4.64	.0071	.258
Sources of Variance				
Reading Level	1	13.42	.0007	
Age	1	0.94	.3387	
Verbal Scale IQ*	1	4.17	.0477	

*Based on Boder Reading Quotient (see text).
**Based on Wechsler Intelligence Scale for Children.

Table 20

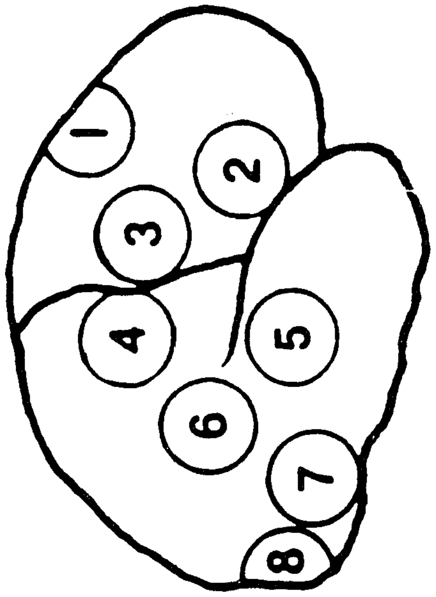
Summary of the General Linear Model and Sources of Variance (Type III Sums of Squares) Predicting Left Hemisphere Activation at Probe Site 6 (Angular Gyrus) from Childhood Reading Level for n=44 Orton Subjects During a Spelling Task (Study).

	df	F Value	P Value	R-Square
Model	4,39	3.53	.0149	.266
Sources of Variance				
Reading Level*	1	8.67	.0054	
Age	1	0.87	.3569	
Verbal Scale IQ**	1	4.46	.0412	
Adult Reading***	1	0.43	.5182	

*Based on Boder Reading Quotient (see text).
**Based on Wechsler Intelligence Scale for Children.
***Based on Finucci Discrepancy Index (see text).

APPENDIX B

FIGURES 1-16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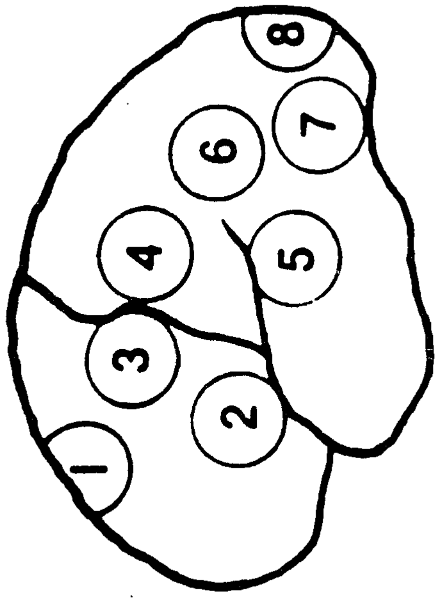
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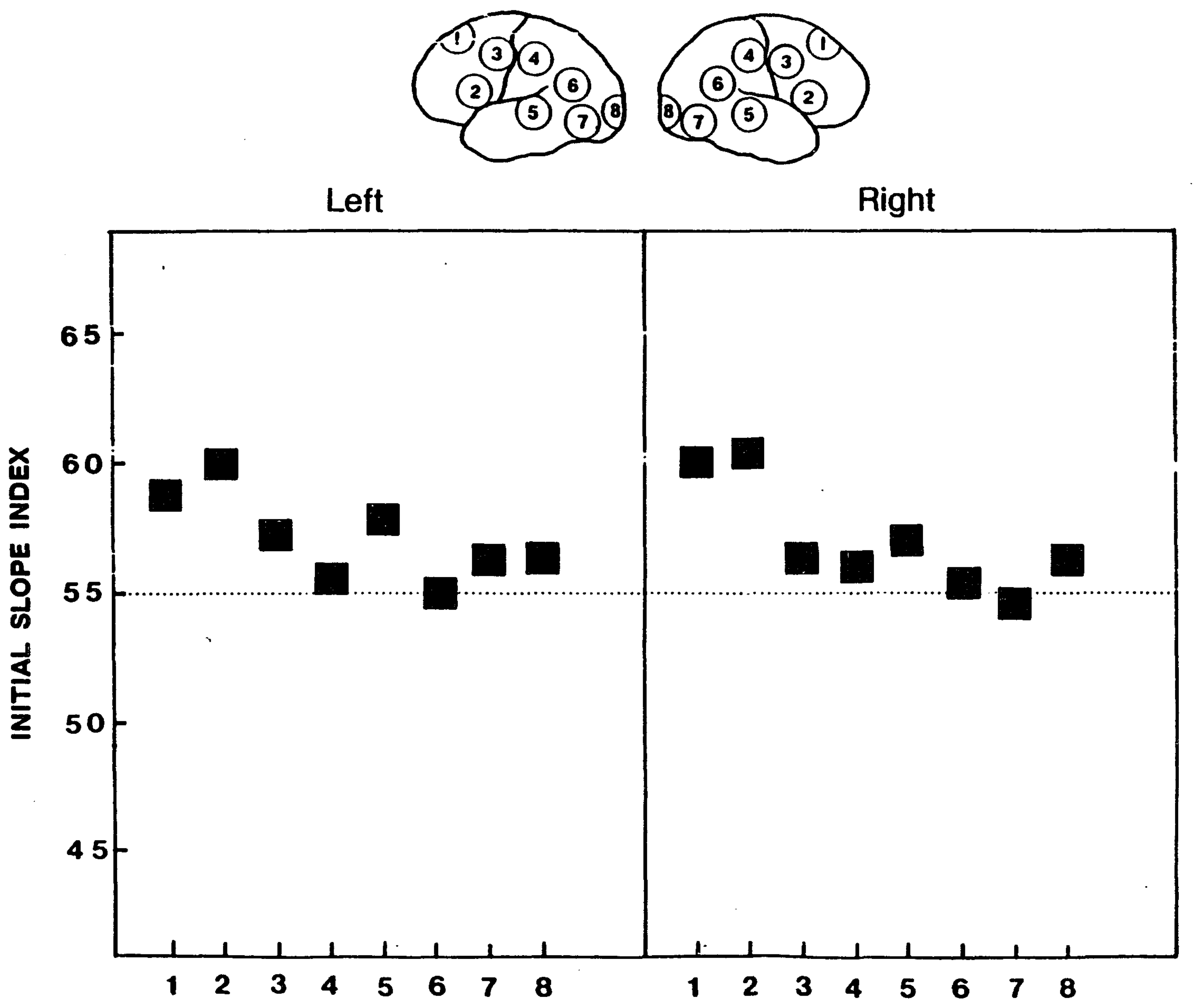
1

<u>Figure 1.</u> Diagram of the placement of eight NaI (T1)-crystal scintillation detectors (probes) on the left and right hemispheres for regional cerebral blood flow measurements: Probe 1: frontal eye fields - Brodmann's 8; Probe 2: posterior inferior frontal lobe - Broca's area; Probe 3: pre-central gyrus - hand-motor area; Probe 4: post-central gyrus - hand sensory area; Probe 5: Wernicke's area - Brodmann's 41 and 42; Probe 6: angular gyrus; Probe 7: inferior temporo-occipital area - Brodmann's 37; Probe 8: primary occipital area.


Left
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INITIAL SLOPE INDEX
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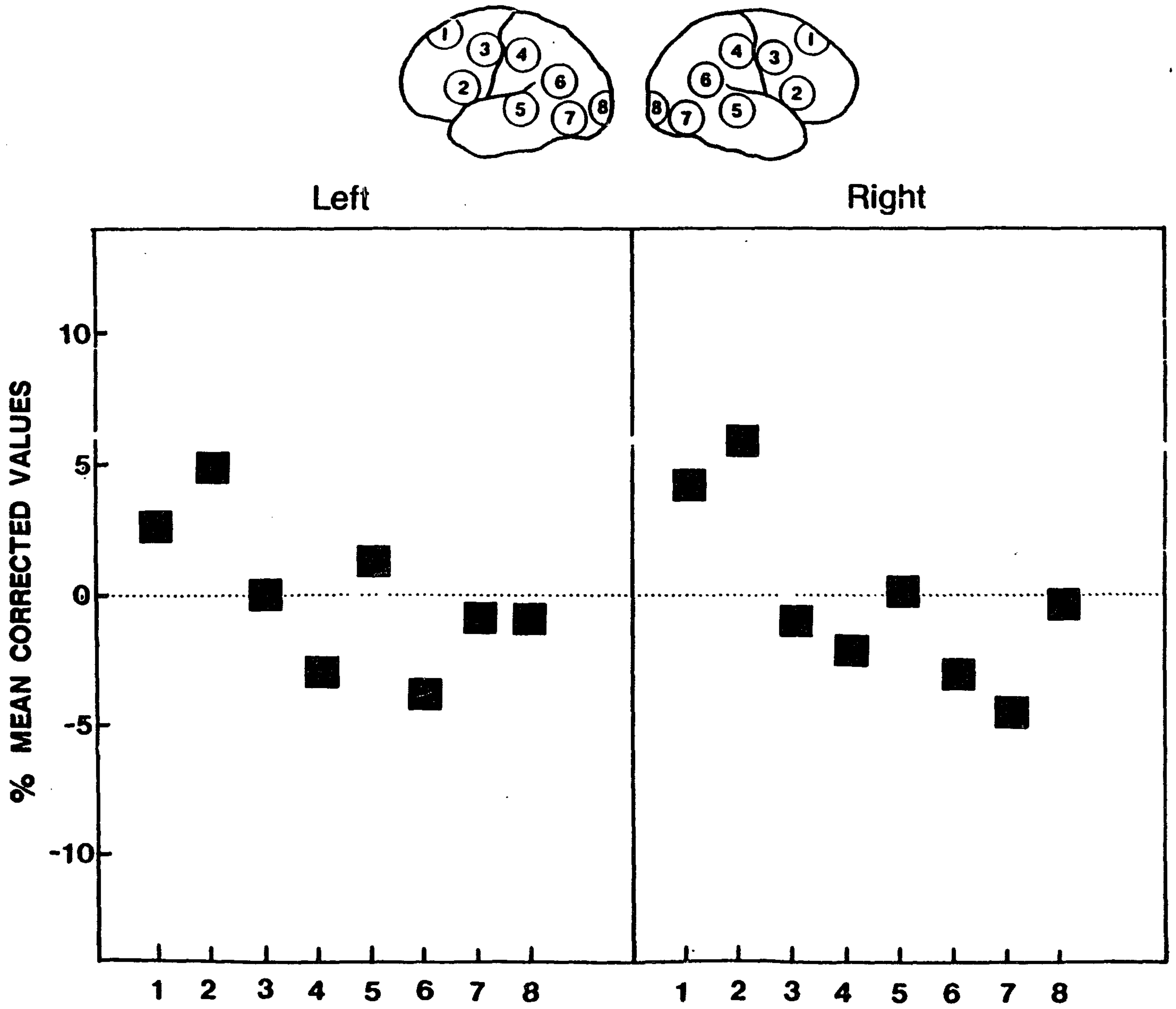
Figure 2. Regional cerebral blood flow profiles of Initial Slope Index measures as a function of probe sites in the left and right hemispheres for normal subjects (n=22) while performing the spelling task (Experiment 1).


Left
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% MEAN CORRECTED VALUES
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5
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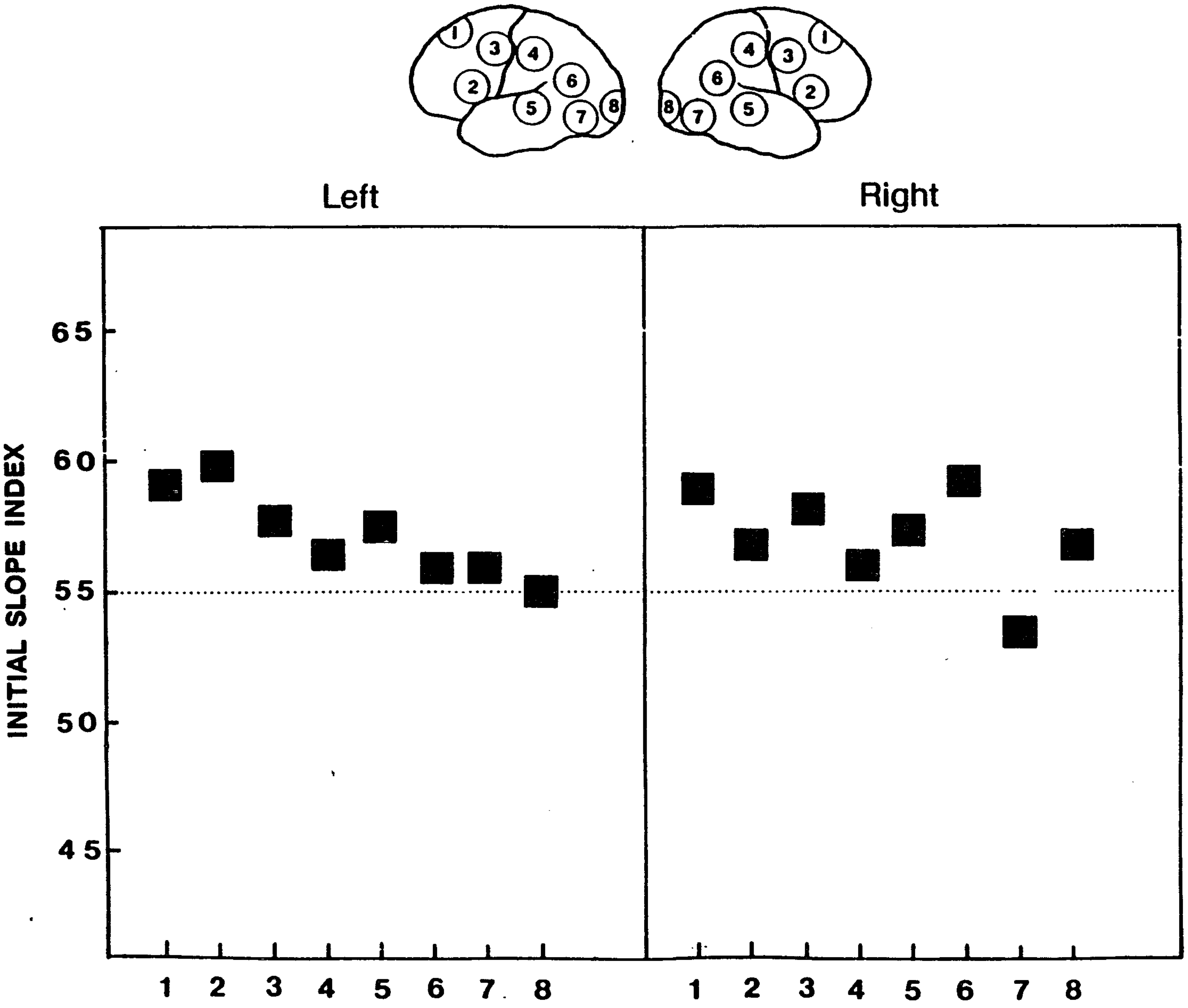
<u>Figure 3.</u> Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for normal subjects (n=22) while performing the spelling task (Experiment 1).


Left
Right
INITIAL SLOPE INDEX
65
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50
45
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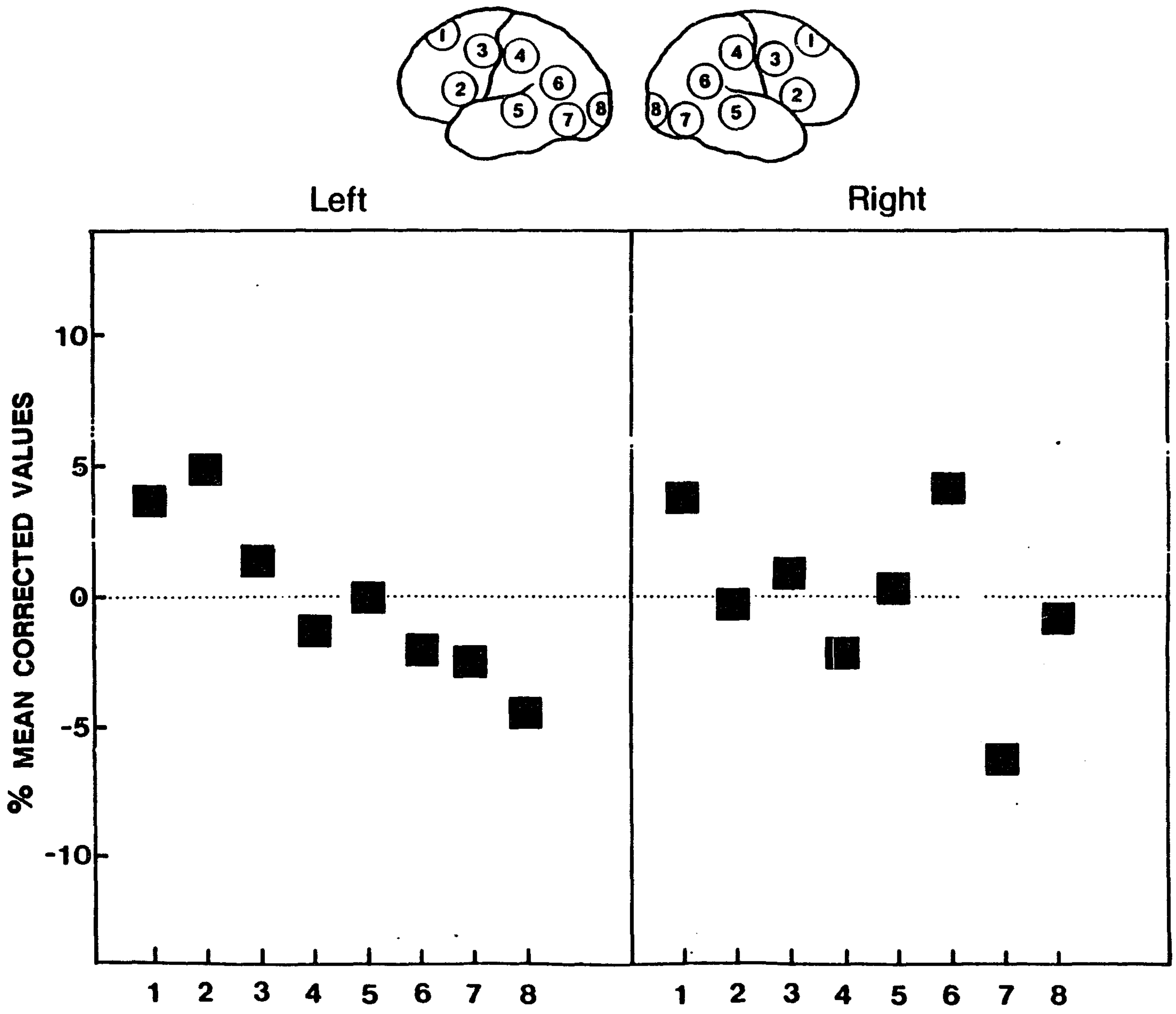
<u>Figure 4.</u> Regional cerebral blood flow profiles of Initial Slope Index measures as a function of probe site in the left and right hemispheres for Orton subjects (n=20) while performing the spelling task (Experiment 1).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3
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7
5
Left
Right
% MEAN CORRECTED VALUES
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5
0
-5
-10
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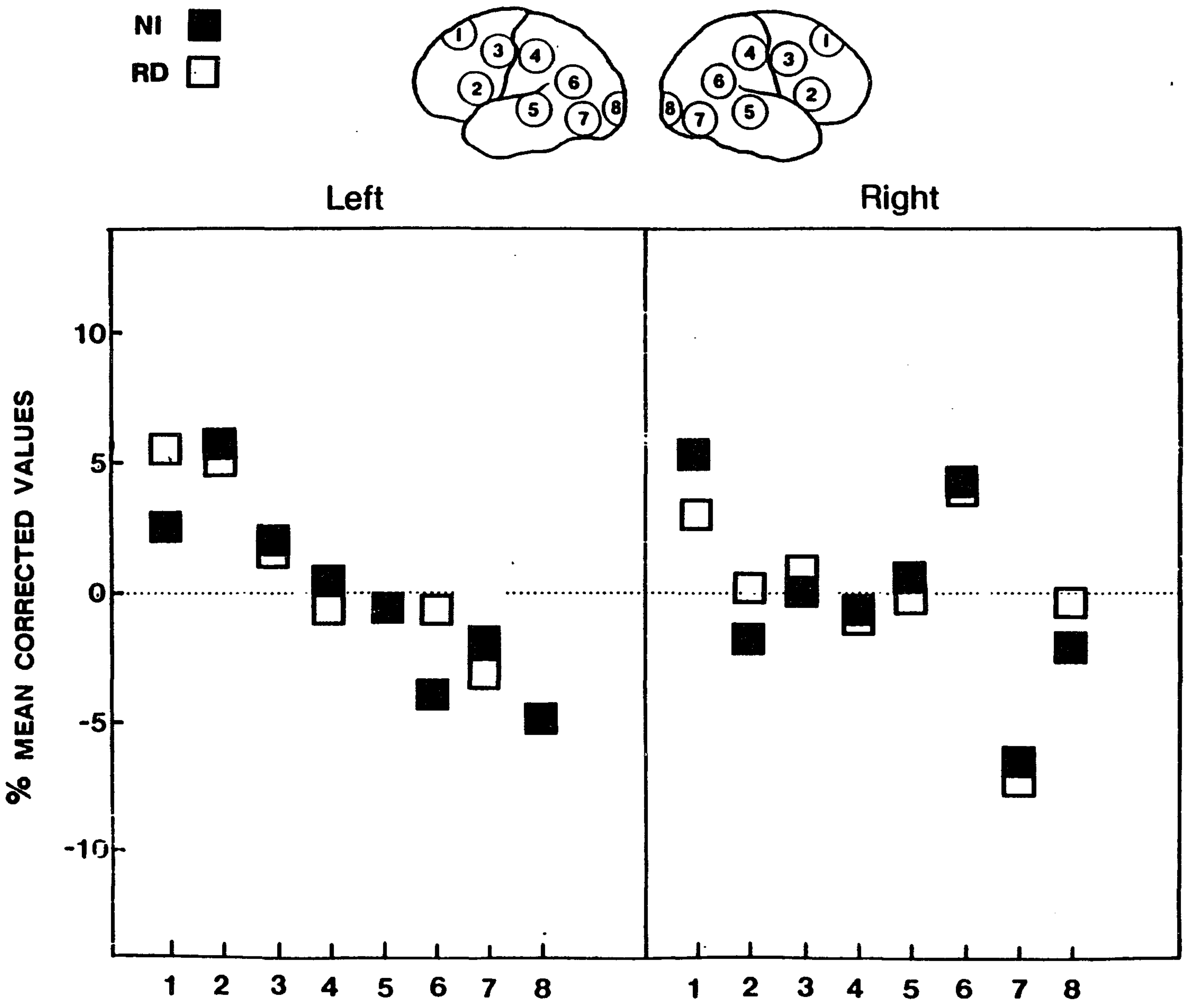
<u>Figure 5.</u> Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for Orton subjects (n=20) while performing the spelling task (Experiment 1).

NI ■
RD □
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2
3
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5
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8
Left
Right
% MEAN CORRECTED VALUES
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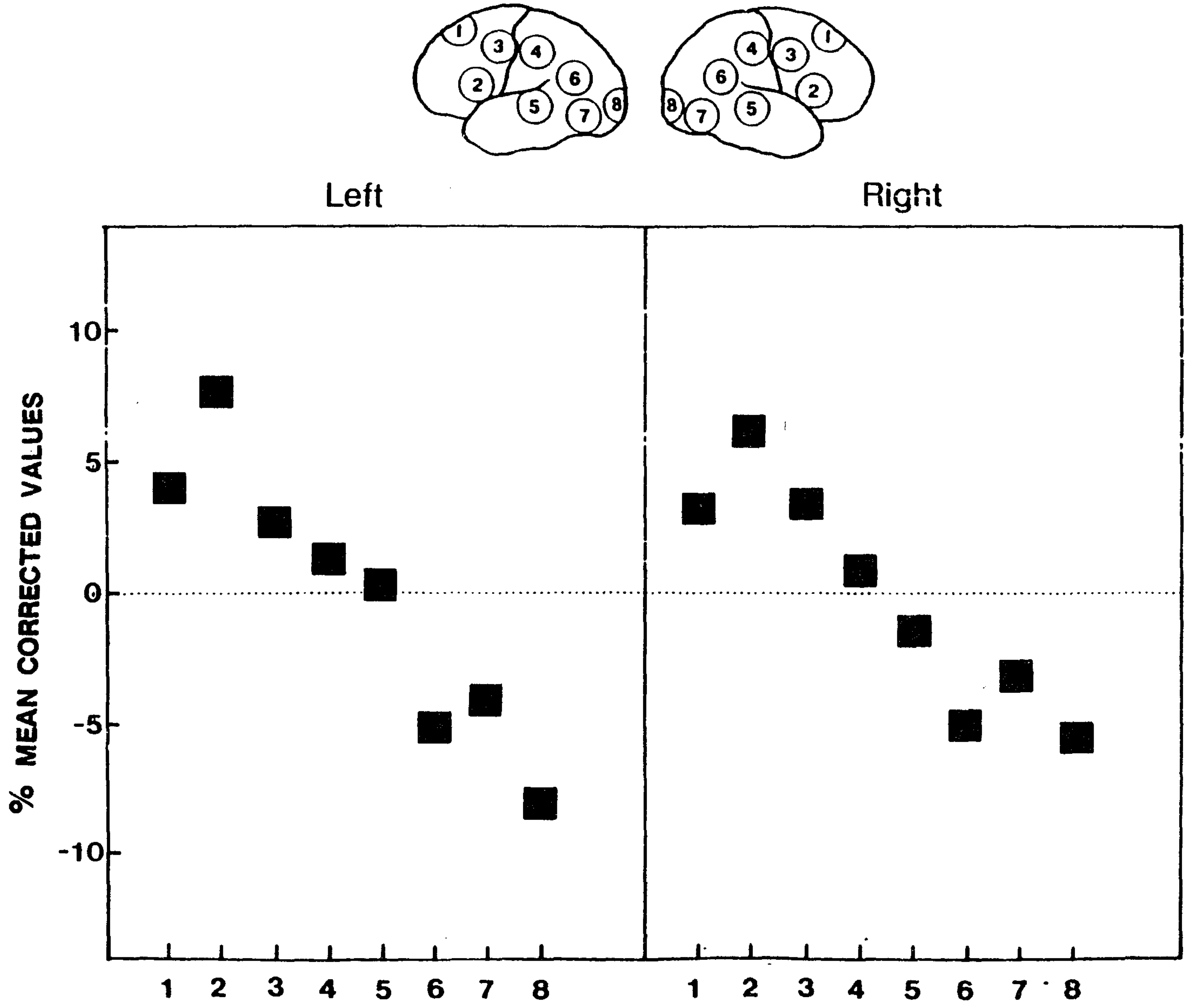
5
0
-5
-10
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8

Figure 6. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for non-impaired (NI; n=6) and impaired (RD; n=13) Orton subjects while performing the spelling task (Experiment 1).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Left
Right
% MEAN CORRECTED VALUES
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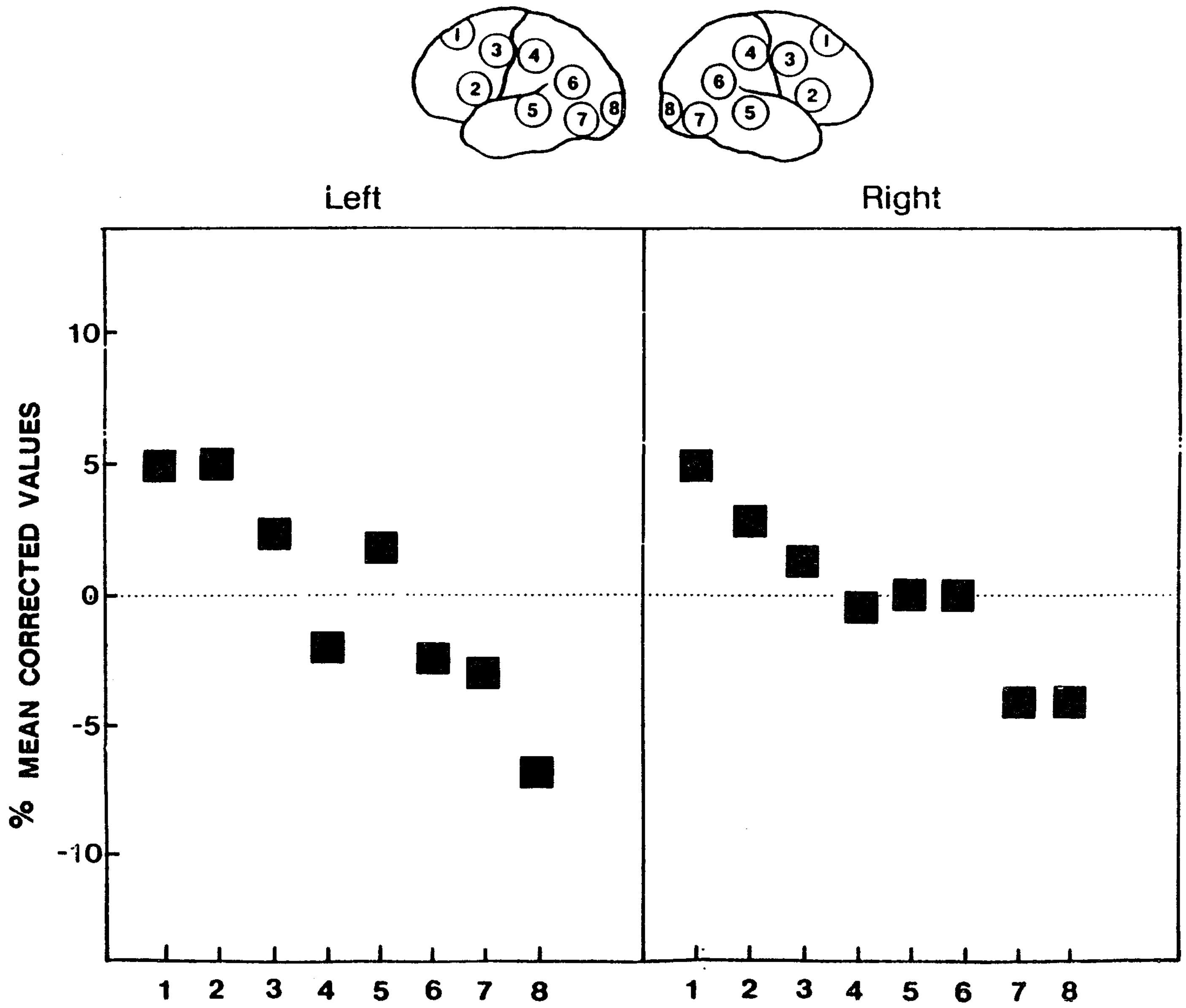
0
-5
-10
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8

Figure 7. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for normal subjects (n=19) while performing the spelling task (Experiment 2-A).


Left
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% MEAN CORRECTED VALUES
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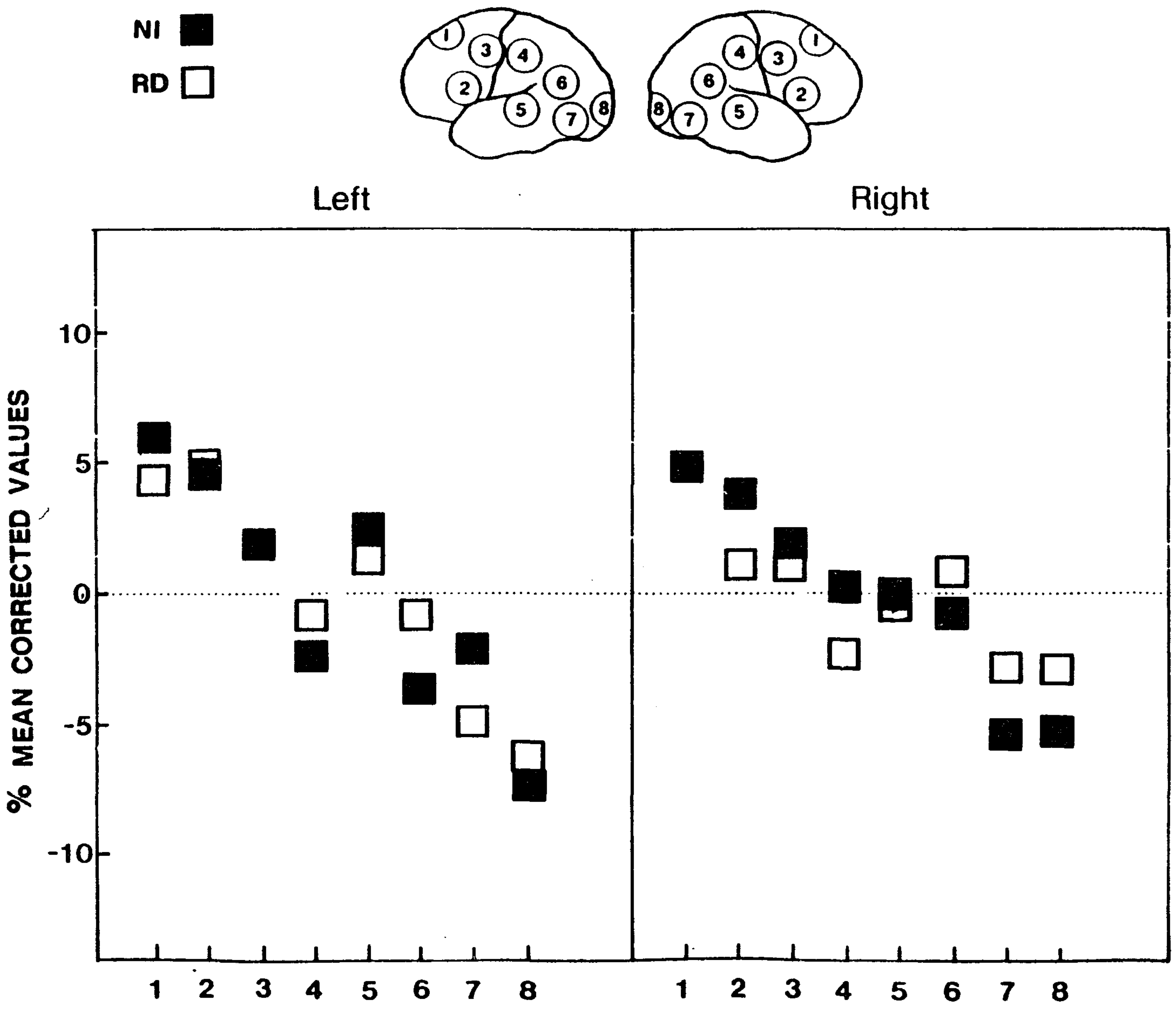
-5
-10
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8

Figure 8. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for Orton subjects (n=27) while performing the spelling task (Experiment 2-A).


NI ■
RD □
Left
Right
% MEAN CORRECTED VALUES
10
5
0
-5
-10
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

<u>Figure 9.</u> Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe site in the left and right hemispheres for non-impaired (NI; n=15) and impaired (RD; n=10) Orton subjects while performing the spelling task (Experiment 2-A).

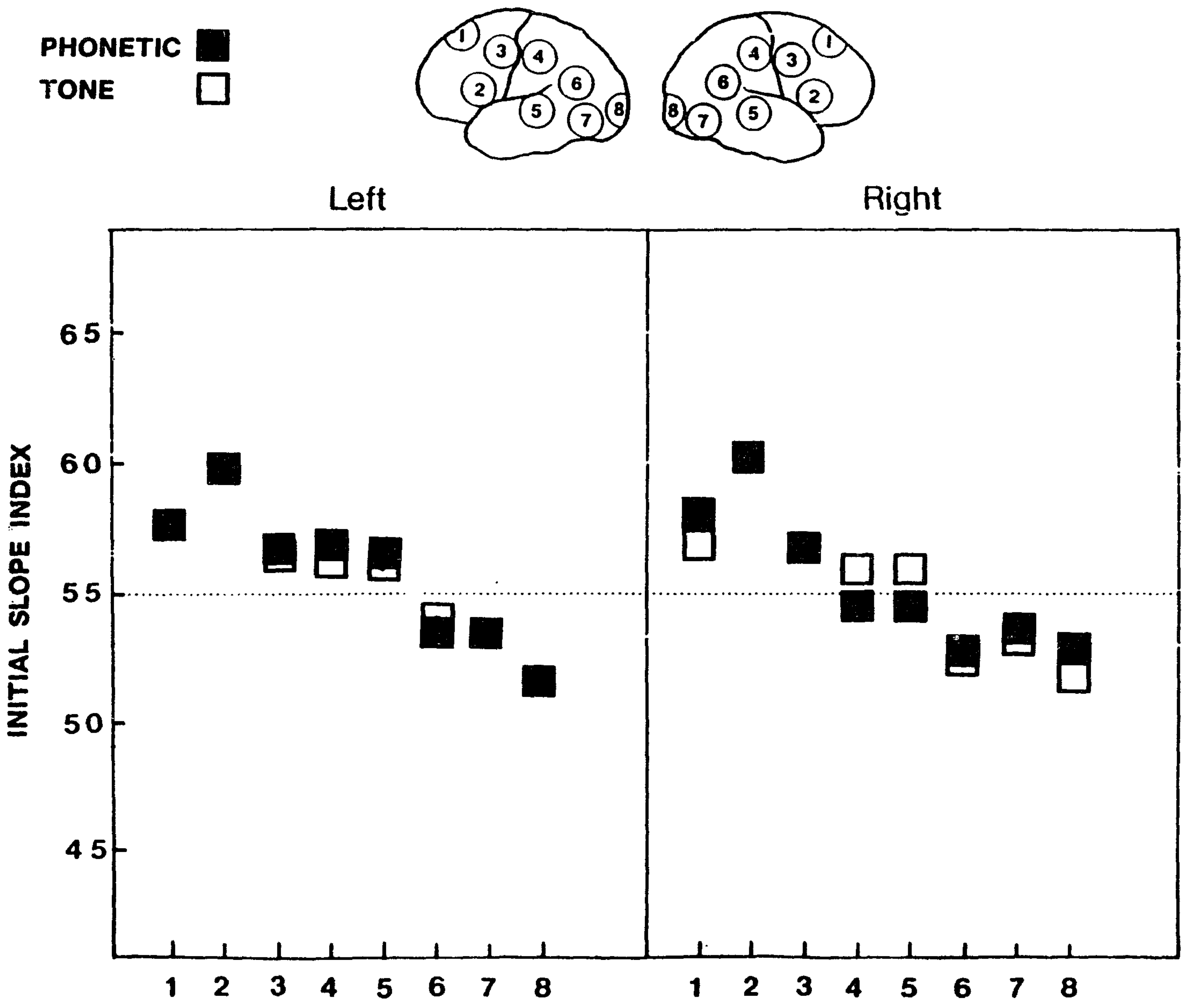

PHONETIC ■
TONE □
1 3 4 2 6 5 7 8
4 3 1 6 2 8 7 5
Left
Right
INITIAL SLOPE INDEX
65
60
55
50
45
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8

Figure 10. Regional cerebral blood flow profiles of Initial Slope Index measures as a function of probe sites in the left and right hemispheres for normal subjects (n=17) while performing the phonetic and tone tasks (Experiment 2-B).

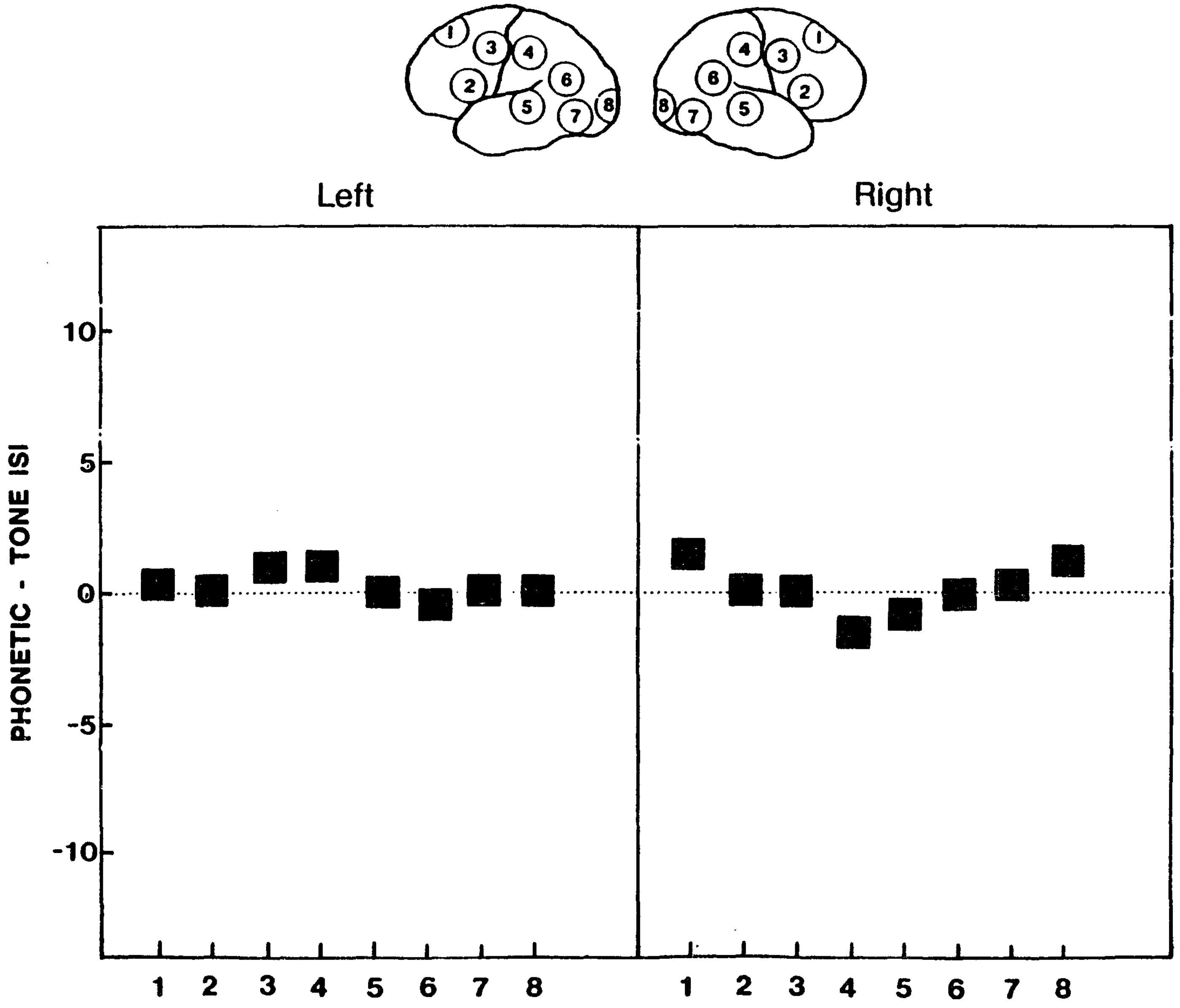

1
3
4
2
5
6
7
8
4
3
1
6
2
8
7
5
Left
Right
PHONETIC - TONE ISI
10
5
0
-5
-10
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

Figure 11. Simple difference between the phonetic and tone task Initial Slope Indices as a function of probe sites in the left and right hemispheres for normal subjects (n=17; Experiment 2-B).

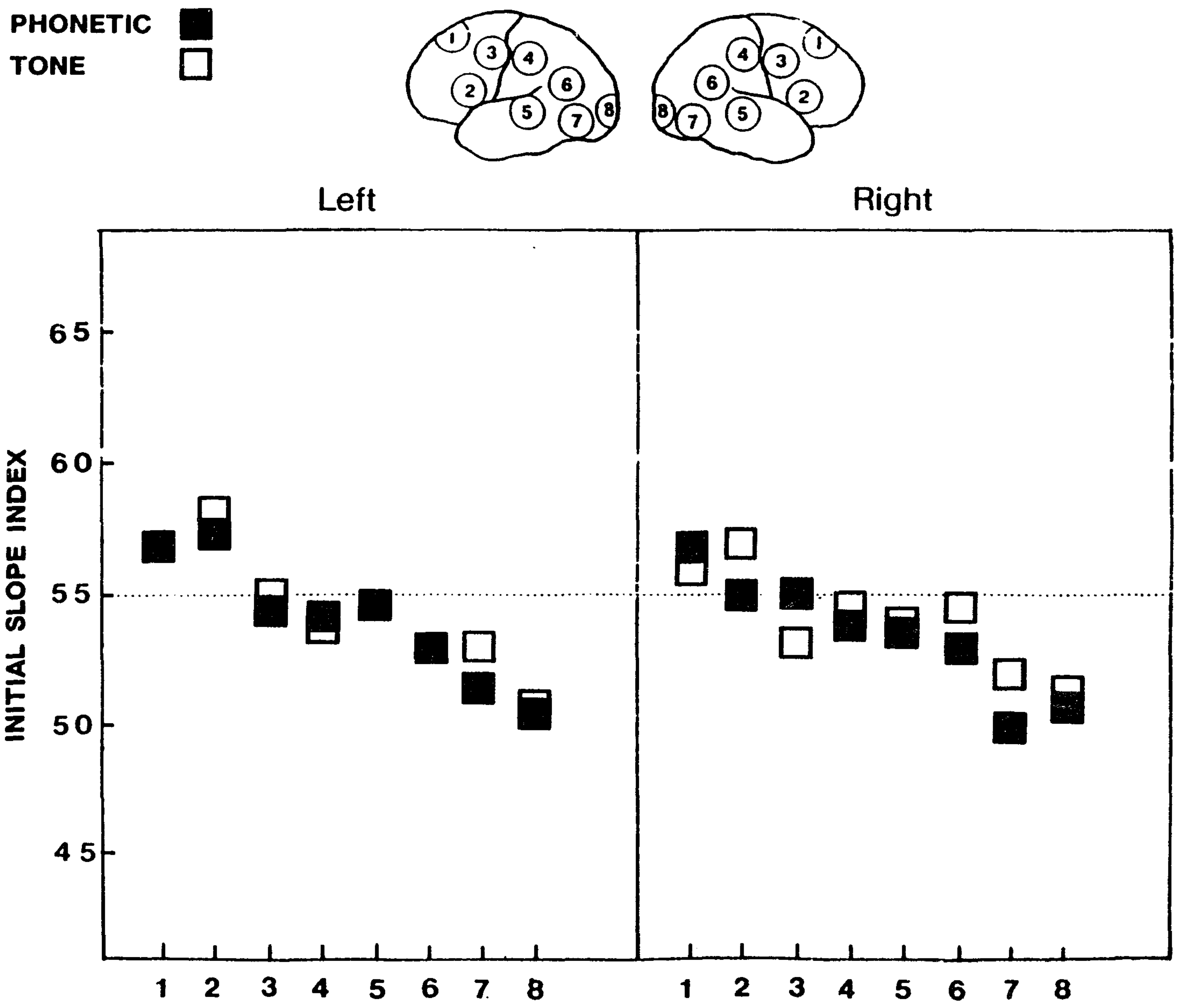
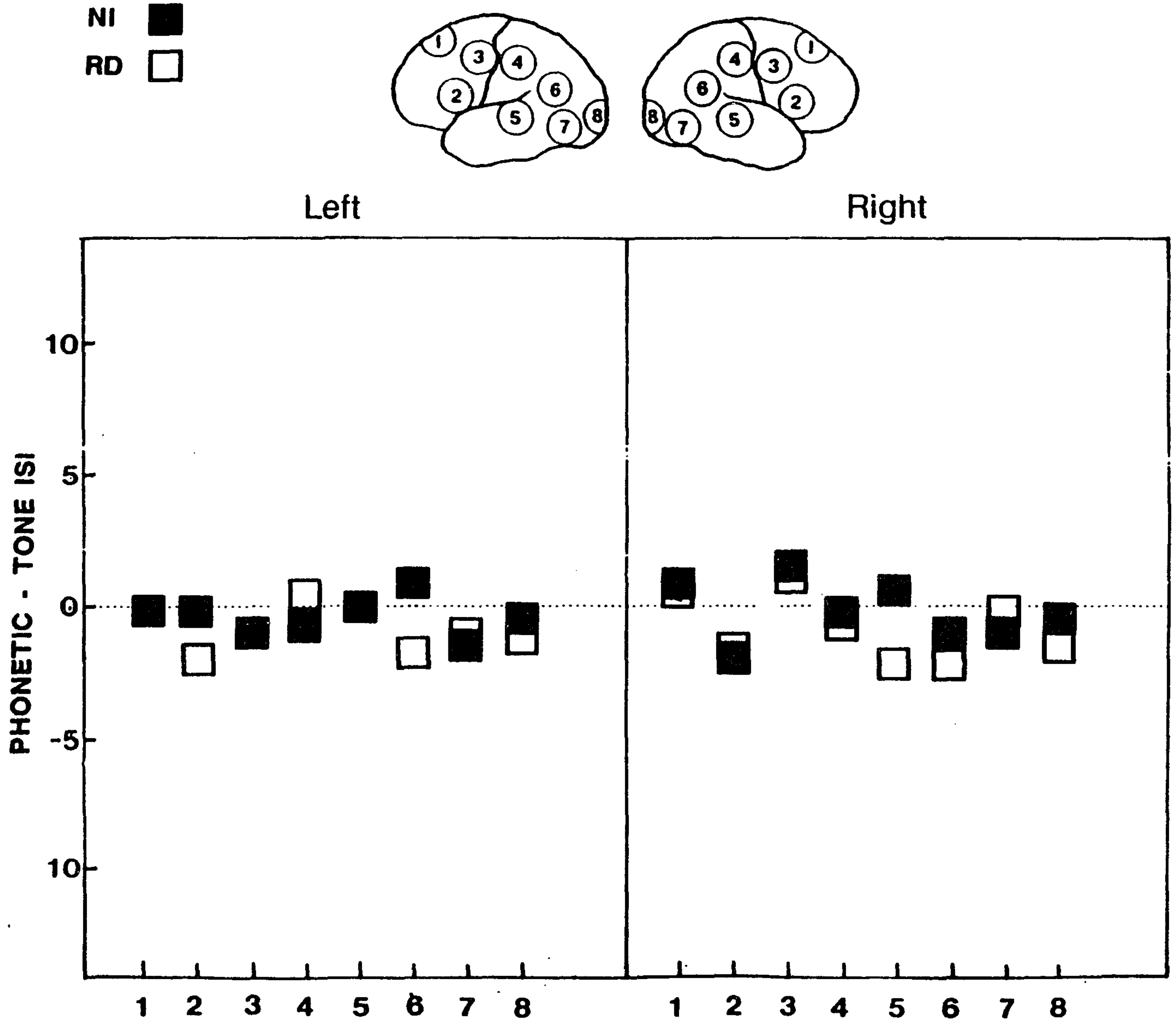

PHONETIC ■
TONE □
1
2
3
4
5
6
7
8
Left
Right
INITIAL SLOPE INDEX
65
60
55
50
45
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

Figure 12. Regional cerebral blood flow profiles of Initial Slope Index measures as a function of probe sites in the left and right hemispheres for Orton subjects (n=27) while performing the phonetic and tone tasks (Experiment 2-B).


NI ■
RD □
Left
Right
PHONETIC - TONE ISI
10
5
0
-5
10
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

<u>Figure 13.</u> Simple difference between the phonetic and tone task Initial Slope Indices as a function of probe sites in the left and right hemispheres for non-impaired (NI; n=16) and reading disabled (RD; n=11) Orton subjects (Experiment 2-B).

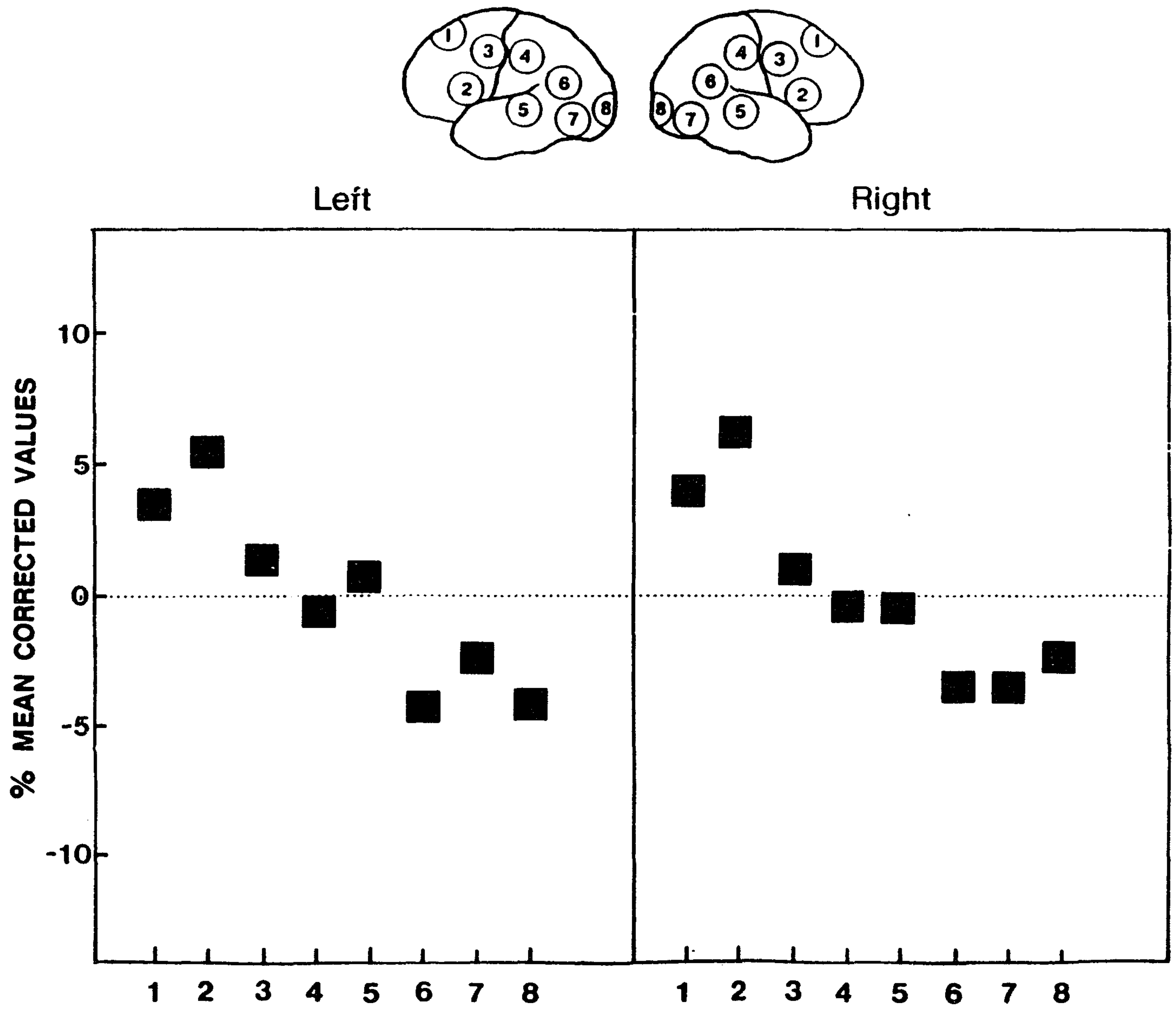
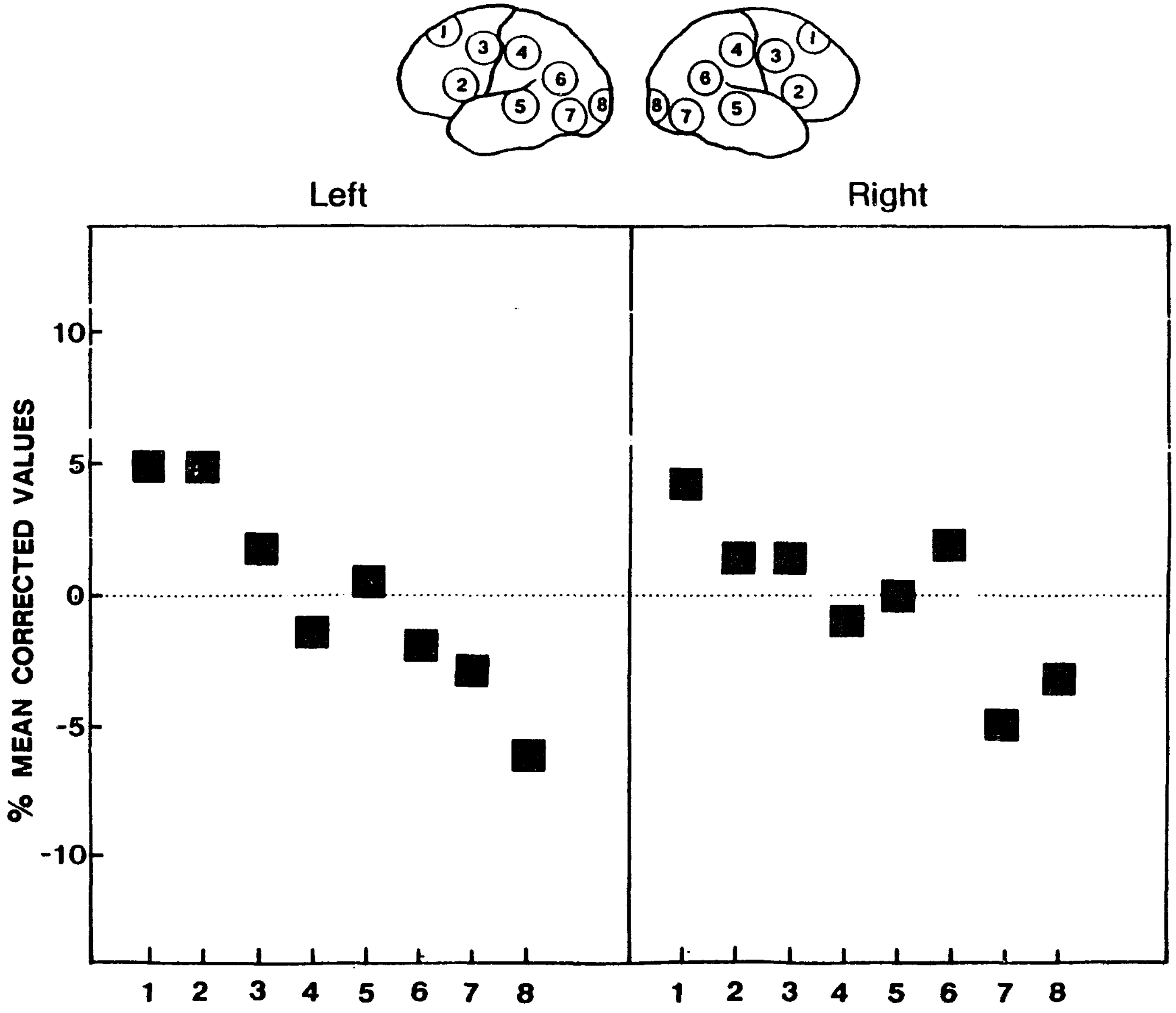

1
3
4
2
6
5
7
8
4
3
1
6
2
8
7
5
Left
Right
% MEAN CORRECTED VALUES
10
5
0
-5
-10
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

Figure 14. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for normal subjects (n=41) while performing the spelling task (Study based on Experiments 1 and 2-A).



1
3
4
2
6
5
7
8
4
3
1
6
2
8
7
5
Left
Right
% MEAN CORRECTED VALUES
10
5
0
-5
-10
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8

Figure 15. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe sites in the left and right hemispheres for Orton subjects (n=47) while performing the spelling task (Study based on Experiments 1 and 2-A).

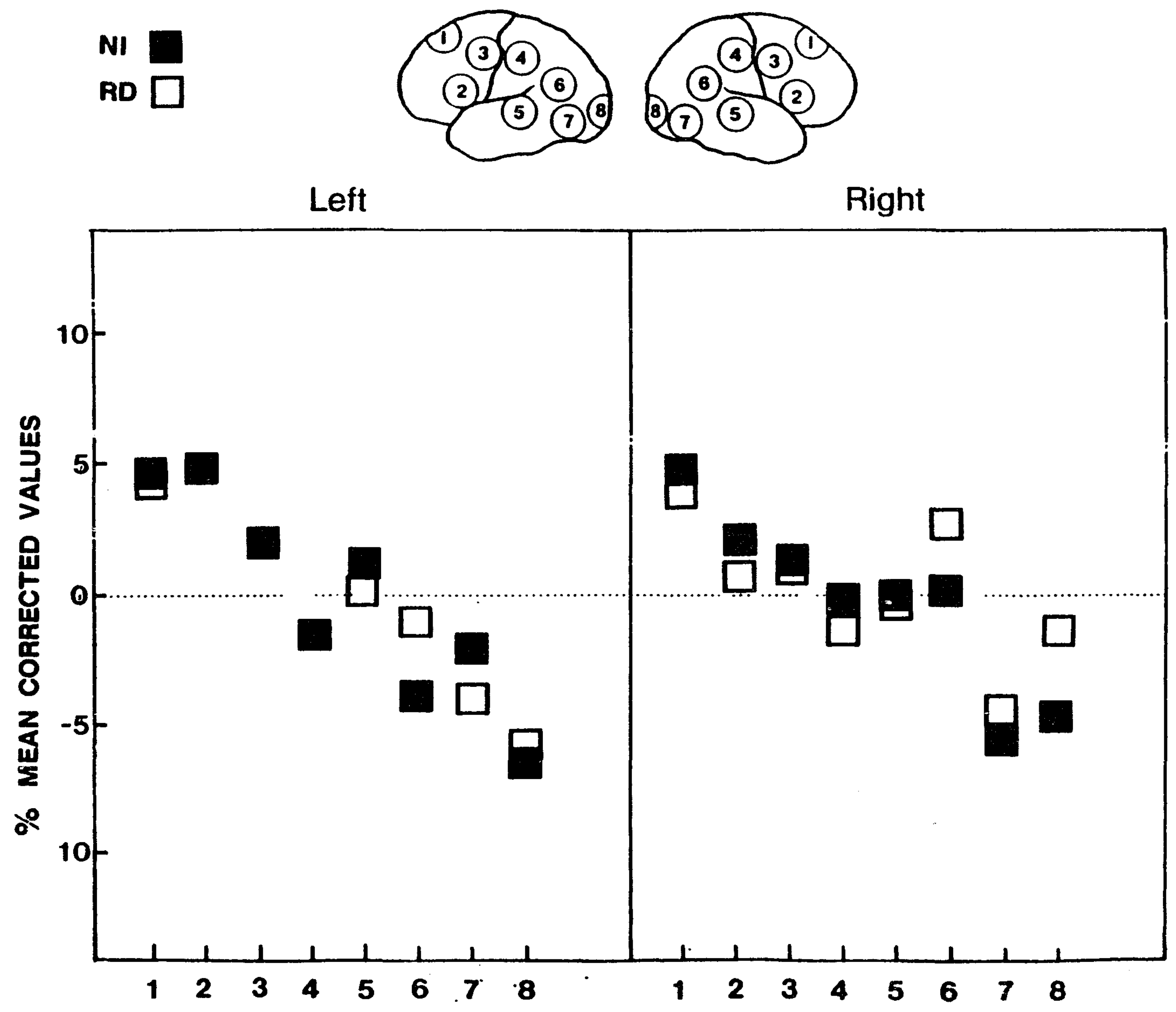

NI ■
RD □
1
2
3
4
5
6
7
8
Left
Right
% MEAN CORRECTED VALUES
10
5
0
-5
10
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8

Figure 16. Regional cerebral blood flow profiles of hemispheric mean corrected measures as a function of probe site in the left and right hemispheres for non-impaired (NI; n=21) and impaired (RD; n=23) Orton subjects while performing the spelling task (Study based on Experiments 1 and 2-A).