

Frontal, temporal and lateralized brain function in children with attention-deficit hyperactivity disorder: a psychophysiological and neuropsychological viewpoint on development

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Abstract

This article considers deficits in the selective aspects of perception underlying symptoms of impaired attention and impulsivity in children with attention-deficit hyperactivity syndrome (ADHD) in terms of frontal and temporal lobe function and cerebral asymmetry. Tomographic studies suggest a disturbed fronto-striatal function, but have neglected limbic contributions under activating conditions and are equivocal on the nature of apparent lateralized differences. Neuropsychological and psychophysiological studies suggest that early and late stages of information processing are affected in both the frontal and temporal lobes and imply impaired intercortical dialog. Given the evidence for a normal specialization in global processing in the right and the processing of details in the left hemisphere, the lateralized impairment may progress from situational ADHD (impaired selective aspects of perception on the right) to pervasive ADHD (additional impairment in decision-making on the left). Accordingly some ADHD children may experience an early negative neurodevelopmental influence that only appears as the brain region matures while others show a delayed development of CNS function. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

1.1. *Subjects: clinical disturbance and function*

A patient with attention-deficit hyperactivity disorder (ADHD) may be mainly restless and impulsive or mainly attention-disordered; but he or she may have both motor and cognitive problems [18]. However, in any series of ADHD patients there are those who also show tics, enuresis and various sorts of learning and conduct disorders. Alongside these, aggression (externalizing features) and anxiety-depression (internalizing features) will be manifest. They all may have potentially confounding correlates in the CNS.

This provides a problem for assessing the results of laboratory studies. Comorbid conditions may be

overtly excluded (e.g. conduct disorders), but sometimes are included, leaving the reader to assess the bias so incurred. A similar problem occurs where ADHD children obtain lower IQ scores than their age-matched healthy counterparts. Is a group matched for IQ and age typical? Is it appropriate to match in this way if such groups mature at different rates, and this contributes to the expression of the condition? Does such a sample of children with a cluster of ADHD symptoms represent the syndrome, at large? These fine details are often overlooked in summary overviews.

1.2. *Schemes for interpreting ADHD symptoms*

Following recognition of the problems of ADHD children in their ability to maintain attention and control impulsivity, Douglas [19] emphasized their difficulty in modulating effort and arousal, and their tendency to respond without waiting for feedback or

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reinforcement. Both features have repercussions in the control of motivation and emotion and directing attention. Barkley's recent review [4] strongly espoused an interpretation of these impairments in terms of executive dysfunction. This is the ability to plan for adaptive response on the basis of experience—to integrate cognitively a variety of events with their possible consequences over time. It is attributed to dorsolateral frontal cortex function on the basis of neurophysiological studies of delayed reinforcement learning in primates and neurological and PET studies of response planning in humans: affect and emotive input and output exert their influence through the adjacent orbitofrontal-amygdala axis [1,84].

However, an emphasis on frontal control may lead to overlooking the other areas and functions with which the frontal cortex is in dialogue to achieve direction and control. For example, the very facilities of arousal and effort (and 'activation'), said by Douglas to be impaired in ADHD children, were the subject of a psychobiological synthesis of animal work over 20 years ago by Pribram and McGuinness [87]. They described three intervening variables that influence information processing: arousal (physiological response to input), activation (tonic physiological readiness to respond) and their coordination through effort. These were attributed to function of the amygdala, basal ganglia and hippocampus, respectively [88]. This background informs the work of Sergeant and colleagues [108,109] who have argued that the crux of the problem in ADHD lies with the application of effort and the consequences for activation and response organisation. Their interpretation plays down the coordinating role of effort on arousal and learning and on search and decision-making. Arguably, this ignores the influences of comorbid features (e.g. anxiety) on adaptive intellectual function. But for the present discussion a potential coordination role in the temporal lobe may be noted; this influences other subcortical regions and, in certain situations, is subject to executive influence.

Another scheme, based on Gray's model [35], proposes that the selective uptake of information in the brain occurs against a background of three competing behavioural systems, the behavioural inhibition system (BIS), the behavioural approach system (BAS) and the flight–fear system (FFS). The BIS is sensitive to secondarily aversive stimuli (innate fear, or extreme novelty) and mediates adaptive inhibitory responses. The BAS is more sensitive to secondarily appetitive stimuli and initiates exploration or approach (food, sexual partners). The FFS is sensitive to primary aversive stimuli and mediates escape or defensive aggression where appropriate. Quay and colleagues argue for a role of the BAS in core symptoms and opposing effects of comorbid internalizing or externalizing symptoms on an underfunctioning BIS [90]. This contrasts with the

aforementioned schemes in emphasising that information processing is primary and motor control follows; that limbic (dys)function precedes (changes in) executive and motor control. Evidence will be considered for the involvement of the structure and function of the frontal and temporal–limbic lobes in the development of information-processing problems in ADHD patients¹.

2. Sources of pathology: structure and function

2.1. Tomography (structure)

Is there direct evidence for differences in brain structure or cerebral activation in ADHD children? If so, then it would provide a shortcut to the functions that psychologists should be examining. In practice, the strategy is usually the other way around. As there are practical limitations to the number of regions one can examine in tomographic investigations, their selection is usually based on neuropsychological evidence of dysfunction.

Early reports of diffuse differences in the brain structure of ADHD children were not confirmed after employing appropriate controls and quantitative assessment [110]. With the introduction of MRI, small ($n = 7-11$) then larger samples ($n = 50-57$) of ADHD boys were shown to have, on average, smaller anterior frontal cortices on the right—the opposite of what was expected [10,12,43]. Measurement techniques became more refined, but even recent work has not reported on groups based on developmental criteria, despite matching for age and sexual development (e.g. Tanner ratings). Is it feasible that the right-sided dysfunction alluded to here, is on the left? Perhaps the amount of synaptic pruning expected at this age has not occurred in the left prefrontal region of ADHD patients. For example, there is a report of decreased metabolic activation in left frontal areas in 14-year-old ADHD patients performing an auditory continuous performance task [131]. While these findings have been dismissed [12,23], there is some consistency with early reports of decreased cerebral blood flow (CBF) in frontal, as well as the primary visual, auditory and sensorimotor cor-

¹ It is beyond the scope of this article to establish what may have given rise to the dysfunctions described. Nonetheless, in the absence of evidence for brain damage it is important to realise that there are two sorts of schemata for explaining the disturbances described. One posits an early negative neurodevelopmental influence that only appears as the brain region matures. This disposition could be of environmental or genetic origin. A second posits merely a delay in neural development that may be expressed in terms of synaptic pruning, growth factor secretion, hormones or enzyme systems necessary for establishing effective intercortical connectivity. Once expressed the former may have more durable effects than the latter.

tices on the left in these patients; while a decrease on the right was reported for the caudate nucleus [58,59,82]. Although the findings of left prefrontal and parietal perfusion were replicated, in view of confounds with developmental age or IQ [113], their presence in other dysphasic children [16,58] and the absence of correlations to externalizing or hyperactive symptoms, their specificity must remain equivocal [54].

There is also disagreement on whether the caudate is normally larger on the left or the right [12,45]. How then should the 'loss' of asymmetry that both groups report be understood? If we accept that the larger caudate nucleus is on the right [12], then the decrease they report on the right is consistent with the decreased blood flow described above. But there is a recent description of decreased pallidal volume on the left in a small group of ADHD boys [3]. These data suggest that it might be more cautious to talk of a bilateral decrease in size. But, further problems remain for an explanation of ADHD in terms of unusual cerebral asymmetry. For example, the callosal area in patients is reported to be reduced specifically in midsagittal [44] or rostral regions [29], in the splenium [107] or not at all [12].

Areas that appear to remain relatively normal in ADHD patients include the temporal lobe (but see reference to the sensory cortices above). Both the size (MRI [16]) and the activity (SPECT [113]) of the temporal lobe and hippocampus are increased slightly on the right in healthy and in ADHD children. Regions of interest have not yet encompassed the brainstem up to the thalamus or major subdivisions of the frontal lobe. (Decreases in cerebellar volume have been reported [10], but such hypoplasias are found in several developmental disorders [82]).

In conclusion, tomographic studies point to a fronto-striatal disturbance in ADHD patients, that may reflect an unusual asymmetry of function, the nature of which remains equivocal. The proposal that it lies with the pre-/orbito-frontal-caudate-thalamic circuit may point to a subtle differentiation from the frequently comorbid tic syndrome, where the parallel supplementary motor cortex-putamen-thalamic circuit may be affected [12,83,115]. Such results should be viewed in the context of normal development, where there is a linear decrease of the volume of the cortex from prepuberty to adulthood [46], an even sharper decline across puberty affecting the basal ganglia [12] and an increase of brain weight across adolescence [6]. These developments reflect the pruning of synapses and dendrites and an increase in myelination [6,42,47].

2.2. Topography (system)

The strength of MRI lies in the three-dimensional resolution of anatomic entities. In contrast, measures of electrical activity show millisecond time resolution, but

poor spatial resolution. Thus, despite intensive development, functional imaging remains more a prerogative of the electrical (and magnetic) recording methods that shall now be discussed.

The EEG has not yet proved of value in delineating sources of dysfunction in ADHD. Many clinicians find the EEG of ADHD children unremarkable in comparison to other features that they or the parents observe [77,116]. Reports of less power in the 8–10 Hz band [21,111] and occasionally in the β -band [8,67] could reflect problems of attention and arousal. These often respond to medication and ameliorate with increasing age [96,126]. Despite advances in EEG evaluation, it is more useful to examine stages of information processing in the averaged stimulus-elicited EEG, the event-related potential (ERP).

The earliest potentials in the brainstem (latency < 10 ms) and the 'midlatency' potentials (< 100 ms) represent the synaptic stages for the passage of sensory information to the cortex. Brainstem latencies asymptote towards adult levels from about 1.5 years [22] and midlatency potentials from about 3 years [85]. While a less orderly progression may appear in children with developmental learning disabilities [63], studies of children with an exclusive diagnosis of ADHD are not known at this time. At the start of processing in the cortices (P1, latency \approx 60 ms) we found latencies were longer in children with tics, but shorter in those with ADHD [70]. The data (here or below) do not support a recent claim that slow conduction velocities are a feature of young ADHD children and attributable to delayed myelination [120].

Negative potentials are typically associated with excitatory processes and positive ones relate to reduced facilitation [105]. The arrival (registration) of information in the cortex is associated with local inhibitory processes (P1). The P1 itself may be similarly gated by prioritised processing of a prepulse just 100 ms earlier (prepulse inhibition, PPI). The following N1 peak represents the excitation (\approx 100 ms) associated with the allocation of a channel for information processing out of the primary cortex [39,122]. The P2 (\approx 180 ms) from adjacent sensory cortex may represent the inhibition of other channels of information competing for attention and further processing [39,70]. Convergent CBF evidence [49] indicates that the allocation of resources and the focusing of attention occurs in the secondary cortices of the superior temporal gyrus. Here too are found the source dipoles of stimulus comparison processes (e.g. the deviant-minus-standard difference-waveform, or mismatch negativity (MMN), \approx 150–220 ms). These are traces representing perceived stimulus differences. Processing then enters an 'endogenous' phase of controlled processing susceptible to conscious modulation. Successive N2 and P3 peaks represent categorisation and target-related information processing, and updat-

ing of the associations [39]. They can be recorded from several limbic and neocortical substrates. In both of the processes represented, the idea of a comparator plays a large role [35]. Frontal, executive control becomes an important feature in directing and monitoring the dialogue essential at this tertiary level of analysis.

The normal development of auditory ERPs from about 8 to 21 years passes through three main stages [73,119]. The most marked is across puberty when an overlying frontal negativity of childhood (Nc) disappears, early peaks show a less diffuse topography and the frontal components become differentially sensitive to the type of stimulus. Topographic shifts are completed in early adolescence (e.g. N1 to the left, P2 anteriorly) and N2 becomes sensitive to attention conditions (diffuse versus focused), reflecting the ability to categorise information. Response times to target stimuli decrease. In late adolescence, P2 develops a reducing response to the type of tone and latencies continue to shorten, reflecting processing efficiency.

Auditory P1 and N1 maxima occur at frontal sites in both ADHD and healthy children [70]. Some laboratories find no size differences in the auditory or visual modality [66,70], others have seen an absence of the small increase in the N1 amplitude, usually seen after a target stimulus in a discrimination (in three modalities, [50,57,99]). These differences probably reflect the pervasiveness of the symptoms in the different groups studied. But already at this early stage of processing latencies may be 20% shorter in ADHD patients [70,101].

In our laboratory, one of the more striking findings has been the larger P2 component in ADHD patients, shared by tic patients with comorbid symptoms of 'attention-deficit' (Fig. 1, [70], for auditory and visual stimuli [33,101]). Some reports describe smaller P2 peaks that normalise with response to psychostimulant therapy [38,89,130]. The difference likely reflects the presence or absence of certain symptom clusters in the ADHD constellation. For example, P2 has been reported to be larger in those with than in those without hyperactivity [41]. We suggested that large P2 peaks are consistent with impulsivity in these children, as we have observed small amplitudes in young patients with obsessive-compulsive disorder who are anything but impulsive [72]. In turn this is consistent with the proposal of fewer inhibitory checks from contextual information (processed in parallel) on the further processing of the stimulus that has caught the subject's attention. This explanation also accounts for the shorter latencies in ADHD patients recorded at later stages of processing, e.g. P2, N2, P3 [70,93,101].

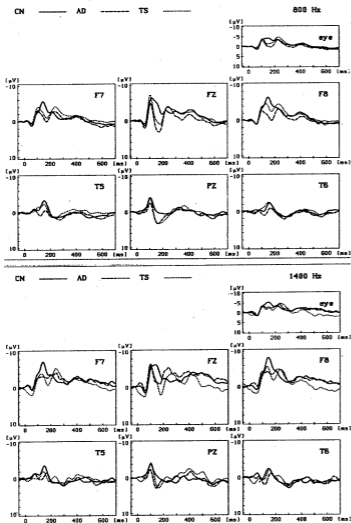
N2 amplitudes, associated with stimulus categorization, decrease with increases of age and focused attention. Then how should one reconcile reports that ADHD patients have smaller N2 peaks than controls after visual [101,106], but larger ones after auditory

stimuli [89,93]? Although the reported age ranges overlap, two studies (using auditory stimuli) found that N2 was smaller in the younger patients, but larger than normal in the older ones [38,98]. This provides a striking parallel to a Kamin-blocking experiment (Section 3.3) where older patients were impaired, but younger ones were paradoxically better than controls in the suppression of learning about information superfluous to the task—a categorisation ability [68]. Thus while several features of ADHD information processing are consistent with developmental delays, a detailed explanation awaits a fuller account of the different stages of normal development, especially in the younger age range relevant for ADHD study.

Subtraction of the waveforms elicited by two different stimuli results in a 'difference wave', a neural trace of a comparator-function crucial to selective information processes. MMN, the dominant negativity 150–220 ms after the stimuli, results from comparing different non-target stimuli (see above). A comparison of target- with non-target-ERPs results in a processing negativity (PN, an attentional trace). Frontal peaks probably reflect generators in the temporal lobe [72]. Generalizing from the experience of four laboratories, the size of neither MMN nor PN is clearly different in ADHD patients. Small increases and decreases at best point to poorer modulation of comparator processes in ADHD patients [50,52,70,100,101]. However, we found a lateralisation for MMN at left frontal sites in ADHD patients that contrasted with a bias to the right in age-matched controls (Fig. 1). (The bilateral adult distribution develops from about 14 years of age [73] and that for tic patients is more posterior.) A report on PN was complex, using both auditory and visual stimuli [100]. Broadly they also found ADHD patients with more PN on the left than controls and attributed this to less negativity in the target-elicited N2 peaks. As MMN is smaller in younger subjects, these data seem less likely to reflect delayed maturation of the mediating structure, but more an anomalous function on the right, consistent with tomographic evidence described above.

Studies in animals and brain-damaged human patients have shown that the temporoparietal border is crucial for the generation of the P3 [62]. The P3 is somewhat smaller in children with ADHD, or dyslexia, autism, tics and other developmental disorders [57,130]. This holds for somatosensory and auditory but perhaps not visual stimuli [50,101]. We noted in a non-task oddball paradigm, with attention sustained, but in a non-demanding way, that the controls had a P3 maximum biased to the right side, as in adults; for the ADHD group maxima were in the midline [70]. As with the MMN, this suggests impaired function on the right, and as noted below, there is evidence of a right hemisphere impairment in other sustained attention tasks.

ERP (P2 at circa 170-200 ms)



MMN (vector-normed maxima)

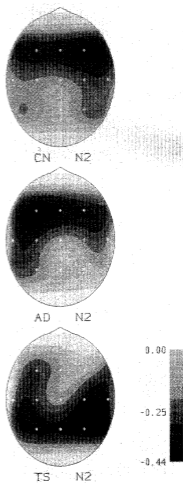


Fig. 1. On the left is shown the ERP for 700 ms after a 800 and a 1400 Hz tone at three frontal and three posterior recording sites on the skull averaged for three subject groups (negativity up, positivity down). The large P2 amplitude is illustrated for the two patients groups vs. the healthy children. On the right the topographical distribution (nose points up the page) of MMN is shown for three subject groups. Healthy children show a right frontal bias (shading) vs. the left sided bias in the ADHD patients. CN, healthy control; AD, ADHD; and TS, tic-syndrome children (details in [46], reprinted by permission of Elsevier).

A slow negative wave develops between a warning and an imperative stimulus (contingent negative variation, CNV). It is more evident for auditory than visual stimuli and reflects anticipation, expectancy and task demands such as effort and sustained attention [13]. Its size is related to cognitive resources and declines with contextual distraction [94]; it is large at central sites, but a drop off over frontal sites is noted in children and in advanced age [20]. The overall amplitude did not differ in selected ADHD patients, yet was biased to the

right, implying fewer resources on the left [129]. But decreases, with no lateralization at frontal sites, were found for those showing much restlessness, poor academic performance, externalizing [2] or tic symptoms [129]. Studies of other slow waves (e.g. motor readiness potential, postimperative negative variation) report less marked frontal contributions and subtle losses of asymmetry that imply right-sided impairments [96]. These changes may be ephemeral, but they recall a delay in terms of the first of the normal developmental stages

described above. They are equivocal as to which side of the brain shows impaired function.

In conclusion, short ERP latencies in ADHD are not consistent with claims for slowed processing and delayed myelination. Rather it seems that information proceeds for further processing with reduced collateral contextual checks on early processing (large P2). Working memory trace formation (e.g. MMN) and the completion of stimulus evaluation (P3) may be deficient in the right hemisphere. This is consistent with selected tomographic findings. It is not clear that the 'impairment' reflects a developmental delay in the sense that parts of the brain in ADHD patients function like those of healthy children at a younger age.

3. Neuropsychology, information processing and attention

A relatively ad hoc position will be taken here, disregarding a separation of sustained from selective attention, and emphasising that the selective aspect of perception occurs from the start [37]. Thus whether the situation concerns continuous performance (CPT), trace conditioning or learned inattention there is a requirement under more or less of an information load for selection of more from less relevant information. ERP work shows that selection occurs in primary and secondary sensory cortices; that it can occur earlier and undoubtedly occurs later in limbic areas where frontal dialogue may influence the outcome. From the previous sections we need to: (a) describe what type of frontal influence is impaired; (b) illuminate the right (left)-sided bias in ADHD dysfunction; and (c) seek clarification on a temporoparietal involvement.

3.1. Frontal lobe involvement

I shall be brief, as the subject has been reviewed recently [4,112]. On the one hand comparative neuropsychology shows that there are signs of poorer frontal function in ADHD patients. On the other hand authors diverge on the appropriate attribution of given psychological processes to particular biological mediation, and the specificity to nosology².

² Neuropsychological tests purport to highlight a definable function as requiring a definable part of the CNS for normal expression in adults. Test validity has usually depended on the deficits recorded after brain damage, but is being refined by various tomographic procedures. Performance deficits in development do not without reason imply damage, merely that the characteristic adult cognitive style has not been achieved. There may be numerous reasons for this ranging from acute or developmental insults through normal or delayed ontogeny to the need to recruit the activity of more CNS systems than the situation allowed (see developmental ERP topography [73]).

The development of some normal frontal functions in groups of 7–8, 9–12 and 13–15-year-olds was charted by Levin et al. [56]. Between the first two groups there was a big improvement in decision-making (card-sorting categories, errors of commission on go/no-go tasks). From 12 years of age hypothesis testing became more refined (20-questions, Tower-of-London) and intradimensional shifting more efficient. Studies of a variety of ADHD patients indeed show impairments in the performance of tasks that are classically claimed to reflect frontal function. These include verbal fluency and recall [25,34,116], trails B [7,112] and the Wisconsin card-sorting test. We also noted unsophisticated 20-questions performance and, for their age, non-adaptive cognitive shifting in ADHD patients (unpublished data). Eight of 12 reports on card-sorting found increased perseveration or that fewer categories were formed by ADHD children (i.e. poor extradimensional shifts; [4]). Barkley attributed some of the variability to the variable participation of more severely affected patients with a family history of the syndrome. But, developmental delay, estimated at 3 years [112], is as likely to be a crucial factor. Many with experience of the test have noted that: (a) patients' performance varies a lot; (b) non-perseverative errors are numerous; and (c) variation is introduced by the experimenter who often has difficulty abiding by the instructions. Nonetheless, a careful study of some 50 ADHD patients (6–13 years) with above normal intelligence showed, after attempting to balance for cognitive abilities, that the patients often had a problem with maintaining set and with fluency [17,91]. As $\approx 40\%$ of these performed more than one standard deviation worse than the norm, the authors suspected executive dysfunction.

However, with the simplicity and consistency of these results, it is often overlooked that temporal lobe function is involved in many of these tests. Thus, the left prefrontal cortex is activated during word generation in healthy adults, but at the same time there is a bilateral decrease of activity in the auditory and superior temporal gyri [26]. Impairments for verbal memory and categorisation in a group of chronic schizophrenics correlated with MRI-determined decreases in the parahippocampal and superior temporal gyri [65]. During card-sorting adults show increases of blood-flow in (left) frontal regions, but also bilaterally in posterior temporal regions [92]. A comparison of patients with MRI-checked hippocampal sclerosis, lateral temporal seizures and unilateral frontal damage reported that both frontal and temporal groups had decreased measures of fluency, and it was the hippocampal group that recorded fewer categories and more perseveration in card-sorting [14].

In conclusion, there are signs of impaired frontal function in ADHD children that may extend to some complex executive functions. But, similar functions may

be relatively intact (e.g. verbal working memory span [114]) or extend outside the frontal domain. The latter would be anticipated by comparison of impaired checking processes in the stop-signal/no-go task [75] and impaired checks in secondary cortices, deduced from ERP recordings (Section 2.2). It may be the dialogue of the frontal with the temporal lobes that gives rise to function and dysfunction. Taking a summary of soft signs as a criterion for deciding on regions of interest for MRI examination can mislead.

3.2. Lateralization and frontal function

It is a common finding in a CPT that ADHD children notice fewer targets (d-prime worse) and often commit more errors (β -criterion worse). The impairment may not deteriorate over time (no especial vigilance deficit), but may reflect a momentary concentration problem [15,74]. By definition the impairments in terms of signal detection are perceptual deficits, although a number of other intervening variables, such as motivation can influence their expression [80]. Deficits are more evident in externally paced tests, vary with the task demands (e.g. CPT-x, or -ax or -double forms [69]) and may be found in a number of other psychopathological conditions in the young and old.

A differential motivational influence on the performance of healthy and ADHD children with externalising problems may be demonstrable [121], but is likely to vary with nosological and demographic variables as well as reinforcement contingency. Immediate feedback on the CPT is perceived as helpful by most young children, but after about 14 years it is perceived as interference (unpublished data). Experience with biofeedback therapy suggests that ADHD children can use and may indeed depend more on the external help [95]. This is seen as an exogenous 'Ersatz' for the weakly-expressed endogenous point of reference necessary for executive control (see also eye movements and fixation point, below). Motivational influences may be a part of the non-specific spectrum of the CPT impairment, as suggested for the CPT deficits in schizophrenia [104]. Studies of brain damage in children and adults [40,125], suggest that an influence of the right frontal lobes in motivation is likely. This conclusion parallels the conclusion of impaired right hemisphere visuospatial function in CPT-impaired ADHD children [27]. It is more parsimonious to describe motivation, like visuospatial abilities, as adjunctive if not integral to a right hemisphere role in perception and attention.

For example, on a self-paced cancellation test, ADHD children made more errors on the left side, implying a right hemisphere source of the problem [124]. Indeed, in PET studies with adults, CPT performance increases blood flow specifically in frontal areas

(e.g. Brodman area, BA 9) and the parietal borders on the right [79]. Reaction time studies during sustained and directed attention confirm the importance of the right hemisphere [25,127]. Indeed slowed reaction times were noted particularly in association with orbital frontal aneurysm [32]. This is of interest in that not only are slowed responses notable for ADHD patients but the orbital-frontal function is so often associated with the integration of affect and emotive stimuli.

Recent PET work showed that the particular province of the right hemisphere lies in global or gestalt perception (Brodman area 18) while that of the left lies in local processing ('the trees for the forest': e.g. the inferior occipital gyrus [24]). This raises the interesting question of whether widespread signal detection problems reflect a dysfunction on the right, while the less frequent signal identification problems, perhaps only in cases with pervasive symptoms, reflect left-sided dysfunction. Recently, a study of the effects of frontal brain damage showed that where patients became more sensitive to irrelevant stimuli (β -criterion increased), MRI images showed that the locus of damage lay in the left superior prefrontal area and in the head of the anterior caudate nucleus [31].

Animal studies are supportive of this scheme, but emphasize the need to look at wider interactions for a full explanation of the neurobiological contributions to these sorts of task impairments. For example, records from prefrontal neurones in monkeys have demonstrated firing patterns in preparation for a response to a target that vary with the difficulty and effort required for a perceptual discrimination [55]. This responsivity is influenced by a dopaminergic innervation with lateralised patterns of receptor distribution (e.g. more D2 sites on the left than the right [28]). In rats, damage to dopaminergic systems results in more omission errors and increased reaction time; a feature that can be counteracted by subthalamic damage at the cost of more errors of commission [5]. Such impulsivity has also been noted after damage to the anterior cingulate area of rodents [64]. In return this result models what we know from human CBF studies: cingulate activation is important in target detection, go/no-go and Stroop performance [78], and dysfunction is thus implied for impulsive ADHD performance in stop-go and Stroop tasks (eight out of nine studies noted in [4]).

Thus, comparative neuropsychology implicates components of the frontal-striatal-thalamic circuit in sustained attention. Indeed early work with rodents noted that individuals that did not show clear side preferences were those that were the most behaviourally active and the poorest learners [30]. Perhaps lateralization, or its absence, within the cortical-subcortical circuit is significant for the appearance of ADHD-like symptoms. An involvement of limbic or temporal lobe elements in the 'decision-making process' is considered in Section 3.3.

First, control of eye-movements so important for directing and maintaining attention will be discussed.

Frontal brain damage in adults often affects the frontal eye field (FEF) and makes it difficult to suppress saccadic eye-movements [25]. A study of the ability of 20 ADHD children to make saccades toward or away (antisaccade) from a target showed no major impairment, but there was a lack of the asymmetry that healthy children showed, with shorter latencies to the left [97]. The implication is that the right FEF functions differently in ADHD (Fig. 2); poor executive control was also implicated in the disproportionate increase of anti-saccade errors recorded when the reference fixation point was switched off. A similar impression was gained in studies of the covert orienting of attention (COA). ADHD children showed more anticipatory responses [9] and a reduced ability to sustain attention to the cued location [118]. The COA task compares reaction times with spotting targets on one side or the other after a cue, that sometimes indicates the false location. 'Exogenous' cues occur at the putative location while 'endogenous' cues (e.g. an arrow) appear by the fixation point. Clear cut group differences are not seen on these tasks [66,81]. But subtle differences in the effect of cue validity relating to the left visual field (right hemisphere function), with respect to control performance, are suggestive of poor executive control of the attention switch [9,36,81]. The pattern shown in Fig. 2 relates to the endogenous condition, and is reminiscent of the FEF result (above), but is opposite to the result with peripheral cues, which may favour children with impulsive tendencies.

In conclusion, global aspects of attention and motivation are under right frontal control, while detailed aspects relating to identification include left frontal function. These functions may be differentially impaired with the severity of ADHD. The context of these experiments concerns two putative attention systems [86]. The posterior one mediates attention shifts; the thalamic pulvinar nucleus is necessary to maintain attention, the posterior parietal cortex allows the disengagement of the attentional focus and the superior colliculus mediates the shift. The cingulate and basal ganglia of the anterior system interact at the executive level designating the priority and allocation of cognitive function. Against this background it may be seen that the evidence touches on poor executive control in ADHD patients, but rarely have subcortical roles been studied. The eye-movement data point to weaker control in the right hemisphere. But, the interaction with medial temporal lobe structures has barely been broached; their function—dysfunction, implicated by ERP data, will now be discussed.

3.3. Lateralization and temporal lobe function

The PET study of adults, on global and local processing (above), also investigated the divided attention situation, that is arguably more pertinent to real life than some of the lab tests discussed [24]. The areas activated were the right temporal-parietal-occipital

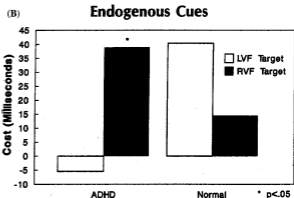
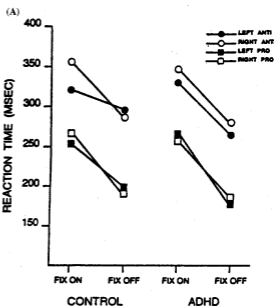


Fig. 2. The upper figure (A) shows the median saccade latencies for error-free trials as a function of ADHD and control group, task direction of eye-movement and presence-absence of fixation stimulus. Note the left-right asymmetry for antisaccades in controls (upper left) that is absent in ADHD patients (upper right) [112]. The lower figure (B) illustrate the costs (reaction time to invalidly vs. validly cued target) for targets in the left and right visual field for ADHD and healthy control children. Note again the absence of the asymmetry shown by controls. (details in [113], reprinted by permission of Elsevier, copyright by the Society of Biological Psychiatry).

junction (BA 39/19) and the left aspect of the posterior superior temporal gyrus (BA 22/39). These are areas implicated in stimulus evaluation processes on the basis of ERP records from brain-damaged adults (e.g. P3, [123]). Temporal lobectomy on the left resulted in larger P2 amplitudes (reminiscent of ADHD). Patients with damage on the right made more errors and traded accuracy for speed. If not exactly like ADHD patients, this is reminiscent of impulsive behaviour [103]. Further, metabolism in the left somatosensory cortex, primary auditory (temporal) cortex and occipital regions was reported to be lower on the left in ADHD [82].

A major component of the medial temporal lobe, the hippocampus, does not achieve mature function in normal children in the first decade. This is one conclusion from developmental studies of trace conditioning [128], a form of associative learning that requires hippocampal function in animals. Both latent inhibition (LI) and conditioned blocking (CB) tests of learned inattention do not achieve mature levels in normal children until the second decade [48,71]. LI is a test of the ability to 'unlearn' that a stimulus has no consequence and acquire an appropriate response to a new contingency. CB tests the normal ability not to learn about a superfluous stimulus added after conditioning to another has started. Both depend on the hippocampus and related mesolimbic structures in animals. ADHD children perform both tasks inadequately compared with healthy age-matched children, but not consistently poorly like younger and older children with complex tics. This provides an indirect argument for a developmental delay in mesolimbic (non-frontal) function [60,67].

Are there other signs for a temporal lobe involvement? There are many reports of poorer recall, especially of non-verbal material, for ADHD patients (e.g. Reye-Osterreith figures [8,34,51]) and those with comorbid tic problems [61]. But often marked differences are not found [91,112]. Kinsbourne pointed out that the problems lay more with the attentionally disturbed than the restless patient [51]. But, as recall tends to be poorer in children of lower IQ, poor performance may merely reflect disorganisation or perhaps a lack of frontal control rather than temporal lobe function.

Lastly, could prepulse inhibition (PPI), as a measure of the gating of the flow of information, implicate temporal function? In this test a click 100–300 ms before a salient stimulus reduces the response to the second stimulus (e.g. startle-blink or P1 ERP). Normal PPI matures between 8 and 12 years of age [11]. In other young patients we found PPI of the P1 component was altered at temporal sites [102], but only the startle form has been used in ADHD, who responded almost normally, showing some 40–50% inhibition [11,117]. However, quite common comorbidities do seem to interfere with gating (e.g. enuresis, tic [11,76]).

If these results are confirmed, the reassuring conclusion may be that the initial flow of information into the sensory cortices is unimpaired in ADHD.

In conclusion, temporal lobe function may not be normal in ADHD—notably on the right in severe cases and less so on the left in others. It is apparent as an impairment of stimulus comparison (difference waves) and is important in making decisions in divided attention situations. It is an appropriate site for executive influences on the prioritising of information processing. Weak influences may be reflected in large P2 ERPs, but only extend to memorial function (medial temporal lobe) if resources or intellectual abilities are otherwise limited or to earlier primary processing (PPI) in the case of complications with comorbid symptoms.

4. Conclusions

Some features of information processing by patients with pervasive ADHD may reflect early neurodevelopmental influences that are not revealed until the structure is mature enough to show normal function [53]. Examples include cases with reduced cerebral activation on the left, especially in situations where fine resolution of detail is required. Other disturbances of information processing are suggestive of developmental delays (e.g. stimulus comparison, MMN; set acquisition, CNV and the ability to categorize). The question of frontal versus temporal lobe involvement is confounded by the need for (frontal) executive function to direct other (temporal or limbic) activity. Depending on the nature of the task this may show up with a frontal bias (e.g. the ability to respond to no-go signals) or a temporal bias (e.g. large P2 response to non-pertinent stimuli). Future studies should recognize that lateralized functional impairments may appear because of the preferred involvement of the right hemisphere in global function and the left in the detail. The ascription of frontal or temporal lobe function—dysfunction to children should be based less on the neuropsychologist's experience with adults and more on the comparative development of specific measures alongside tomographic—topographic backup. Such comparative work requires 'comparison' groups matched for biological development and ability, as well as contrasting age and comorbid pathology.

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