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Behavioral and Psychophysiological Markers of Disordered Attention

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Behavioral and psychophysiological assays provide the most sensitive indication of whether a presumed neurotoxin has a deleterious effect on the nervous system. The effects of lead on the nervous system are strongly suggestive that this agent can produce disturbances in attention; moreover, there are clinical reports of such effects. The action of lead is also manifest in behaviors described as "hyperactive," or reflecting "minimal brain damage." The core symptom in both disorders is probably impairment in attention. The recent Diagnostic and Statistical Manual (DSM-III) of the American Psychiatric Association uses the term Attention Deficit Disorder to replace such terms as hyperactivity and minimal brain damage. Prior studies of the behavioral toxicity of lead may have used inadequate or incomplete assays of attention; this could in part account for the variability in outcomes. Recent research on attention suggests that it is a complex behavior consisting of a number of elements or components, each of which may be in part dependent upon a different region of the central nervous system. Behavioral assays should examine the components of attentive behavior using tests which are sensitive to the different elements. It is recommended that psychophysiological assays (using cognitive event-related potentials), although more difficult and costly to implement, be used as well. These assays may provide a more dynamic view of altered information processing in the brain and help to localize and characterize the behavioral impairment.

Introduction

Many of the contributions in this symposium have pointed to the necessity of conducting behavioral assays of central nervous system functions that are presumed to have been compromised by toxicants. It is essential to assess the behavior carefully and thoroughly, using standardized tests if at all possible. The study by Needleman and colleagues (*1*) of the behavioral effects of elevated dentine lead levels is a model in this regard. Standardized tests will permit comparisons to be made between the group that has presumably been damaged and other groups of subjects with disorders of different etiologies.

In our research, we routinely assess patients and control subjects with a comprehensive battery of neuropsychological and psychometric tests designed to tap a wide variety of behavioral functions (Table 1). Specific references to most of the tests in the battery can be found in Mirsky and Duncan (*2*) or in a later section of this paper.

Tests measuring some aspect of attention are of special importance for the present discussion because it has been suggested that a number of the biological models used to measure the effects of lead (and other neurotoxic agents) might also be relevant to human disorders of hyperactivity or minimal brain damage (MBD). This is the case for the models presented by Hoffer and Altman in this symposium and is suggested in McEwen's discussion of the effect of pseudosteroids. The core issue in both hyperactivity and MBD is attention deficit; in the third edition of the diagnostic and statistical manual of the American Psychiatric Association (DSM-III), the terms hyperactivity and MBD are replaced by the term Attention Deficit Disorder (ADD), as this is viewed as the key symptom:

> The essential features are signs of developmentally inappropriate inattention and impulsivity. In the past a variety of names have been attached to this disorder, including: Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Brain Dysfunction, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction. In this manual, Attention Deficit is the name given to this disorder, since attentional difficulties are prominent and virtually always present among children with these diagnoses. In addition, though excess motor activity frequently diminishes in adolescence, in children who have the disorder, difficulties in attention often persist (*3*).

In a later section of this paper, I shall return to the issue of behavioral assays of attention.

Psychophysiological Assays of Attention-Information Processing

In recent years there has been a substantial amount of cognitive psychophysiological research applied to attention, or information processing, the term which is favored by many cognitive psychologists. These EEG-derived measures appear to hold great promise for the

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Table 1. NIMH[a] laboratory of psychology and psychopathology neuropsychological assessment battery.

Function	Test
Executive	
Sequencing, attention	Trail Making Test
Attention	Stroop Test; Letter Cancellation Test
Perception and reasoning	Raven Standard Progressive Matrices
Concept formation and abstraction	Wisconsin Card Sorting Test; Category Test (Halstead)
General intelligence	Wechsler Adult Intelligence Scale—Revised
Language	
Initiation	Controlled Oral Word Association Test
Lexical	Boston Naming Test
Written	Boston Diagnostic Aphasia Examination—Narrative Writing
Comprehension	Token Test (Spreen and Benton version, 1969); Goldberg Semantic Aphasia Test
Auditory discrimination	Wepman Auditory Discrimination Test
Memory	
Global	Wechsler Memory Scale
Recent verbal memory	Buschke Selective Reminding Test Rey Auditory-Verbal Learning Test
Recent visual-spatial memory	Recurring Figures Test (Kimura) Rey-Osterrieth Complex Figure Test
Remote memory	Boston Famous Faces Test (short form) Television Test Boston Recall Test (short form)
Motor functions	Purdue Pegboard Test Boston Apraxia Test
Orientation	Temporal Orientation Test (Benton)
Personality	Minnesota Multiphasic Personality Inventory
Sensory and perceptual	Bioptor Vision Tests Dvorine Pseudo-isochromatic Plates Titmus Stereo Tests Harris Test of Hand Dominance Eye Dominance Test
Vigilance	Continuous Performance Test
Visual-spatial	Hooper Visual Organization Test Embedded Figures Test (Witkin) Butters' Embedded Figures Test

[a] National Institute of Mental Health, Bethesda, MD.

future of neuropsychological assessment, since they are based on data recorded during behavioral paradigms that tap aspects of attention, learning, and memory. These methods of cognitive psychophysiology are based on patterns of brain waves recorded from the scalp. Whereas EEG patterns reflect the brain's background activity, event-related brain potentials (ERPs) show how the brain responds to environmental events (hence the term "event"-related). ERPs are transient voltage fluctuations generated in the brain in conjunction with sensory, motor, or cognitive events. Plotted on a graph, the ERP comprises a series of positive and negative voltages that occur with different latencies following an event.

At present, ERPs provide the only available window on the neurophysiological transactions of the human brain as it processes information on a millisecond-to-millisecond basis. The ERP is a major source of information about the neural bases of perception and cognition by virtue of its strong correlations with a wide variety of processes, including psychophysical judgments, perception, selective attention, recognition, decision making, expectation, memory, orienting responses, and specific language functions. Such correlations have been observed for a number of ERP components, including N100, N200, N400, P165, P300, and contingent negative variation (*4*). The earlier negative components (e.g., N100) are thought to reflect sensory processing, although some effects of attention can be demonstrated as well. A lexicon of ERPs is evolving, designed to measure a wide array of dynamic patterns of information transactions within the brain that occur in conjunction with specific perceptual and cognitive processes. The availability of these dynamic techniques has begun to enrich immeasurably our knowledge of the way in which information processing occurs in the brain of a particular subject, whether pathological or normal. Therefore, the application of ERPs can add to our information about the cognitive processes by which various tasks are undertaken and the relative timing of those processes.

The application of these methods to the study of the effects of toxicants should be productive. There are two ERP components, among a number of others, which appear to hold special promise for the assessment of attention: The mismatch negativity, or MMN, occurs when a stimulus does not match a previous repetitive series of stimuli. MMN is an early, preattentive measure, apparently indexing what the cognitive psychologists refer to as automatic information processing (*5*). The second component, or P300, is firmly linked to attention, expectancy, and memorability (*6*), or effortful or controlled information processing in the lexicon of the cognitive psychologists. The P300 may be of special interest for the present discussion since there are data to support the view that this ERP component is in part generated in the hippocampus (*7*). If hippocampal cell loss is one of the manifestations of lead intoxication (*8,9*), the P300 could be an index of the central pathophysiology of this toxicant. Figure 1 shows the ERP

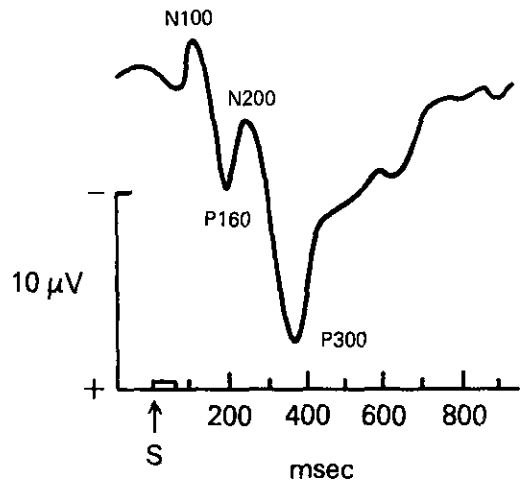

FIGURE 1. Event-related potential (ERP) derived from human scalp recording, elicited to an auditory stimulus (S) to which the subject's attention has been directed. The amplitude of the P300 component indexes attention allocation, task demands, expectancy, and memorability. The latency of this component indexes stimulus processing time and is positively correlated with age (*6*). Figure courtesy of C. C. Duncan (*10*).

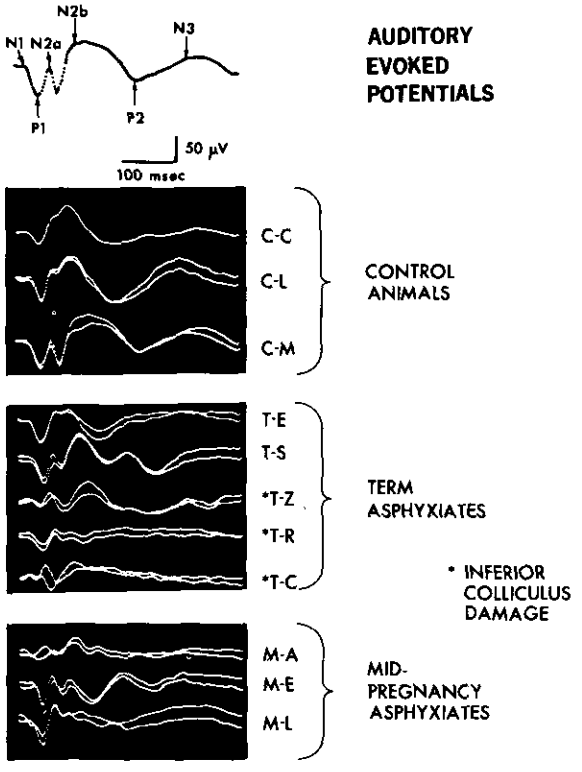

FIGURE 2. Auditory evoked potentials or event-related potentials (ERPs) to an 82-dB ½-sec click source. Also included are ERPs from T-C, a term asphyxiate with extensive brain damage, including bilateral destruction of the inferior colliculi. The total sweep time depicted is 425 msec; in each case the wave form represents an average of 200–300 samples. Note the relatively flat ERPs for the three animals with inferior colliculus lesions (T-R, T-Z, and T-C and for M-A) and the generally reduced amplitudes of all asphyxiates (*12*).

recorded from the scalp, elicited by an attention-demanding stimulus in a special psychological test paradigm.

The MMN appears between 50 and 200 msec poststimulus (given the appropriate task); the P300 appears between 250 and 400 msec (under appropriate task conditions). The P300 (Fig. 1) is better known, and is significantly reduced in amplitude in various clinical states where attention impairment is a key symptom [i.e., schizophrenia (*10*); eating disorders (*11*); dyslexia (Duncan, personal communication)].

Some other examples can be provided of the use of event-related potentials in the investigation of variables relevant to this symposium. The first example is from an animal model study that examined the effects of perinatal asphyxia on behavioral and electrophysiological measures in the monkey (*12*). In this investigation, monkey fetuses were subjected to experimental asphyxiation (produced by compression of the umbilical cord) at one of two periods: at term, or in the second trimester of prenatal development. Figure 2 shows the results of the measurement of auditory ERPs in the three groups of subjects: control, animals asphyxiated at term, and those asphyxiated at midpregnancy. As the figure shows, asphyxia produced reduced amplitudes and delayed latencies of the early negative components of the ERP (presumably tapping sensory processing effects) in all of the experimental animals. Moreover, the effect was especially pronounced in animals whose brains showed evidence of cell loss in the inferior colliculus. That such cell loss occurs with asphyxia would be expected from the studies of Ranck and Windle (*13*) and Myers (*14,15*). These investigators showed the sensitivity to asphyxic insult of this brainstem auditory nucleus, presumably as a result of its high oxygen requirement (*16,17*).

We turn now to examples of the application of cognitive ERPs to human subjects suffering from various types of cognitive impairment. The P300 wave, in particular, has been studied in a variety of populations suffering from some obvious developmental disorder or thought to be at risk for developing some disorder. Populations studied include children with ADD (*18*); children with infantile autism (*19*); the offspring of schizophrenic parents (*20*); the children of alcoholic parents (*21*); and adults who were diagnosed as dyslexic, with or without concomitant attention deficit disorder, as children (Duncan, personal communication). Figures 3 and 4 present some preliminary results of the latter investigation. The ERP measures appeared to distinguish between the two dyslexic subgroups and between these two groups and the controls. All subjects were male. Dyslexics who were diagnosed as likely to have had Attention Deficit Disorder (ADD) as children had a reduced voltage of the P300 wave in central cerebral locations (Fig. 3) as compared with normal control subjects. In contrast, those adult dyslexics who were di-

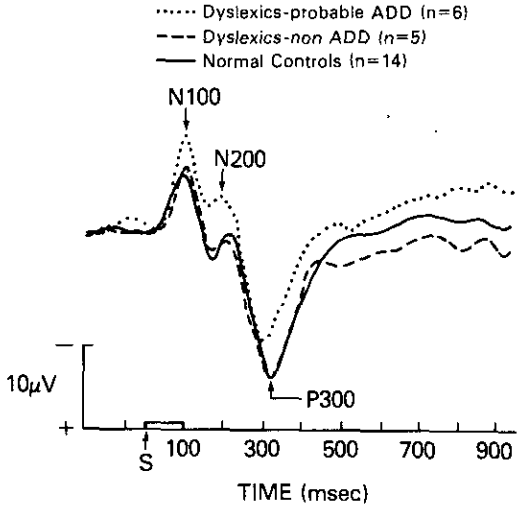

FIGURE 3. Auditory ERPs from the central midline (Cz) placement in normal control subjects and in two groups of adult dyslexics: those with, and those without a probable diagnosis of ADD in childhood. The ERPs were elicited in the course of an auditory reaction time task. The non-ADD dyslexics are not distinguishable from normal controls by this measure, whereas those with probable ADD have a P300 that is reduced in amplitude (from Duncan, personal communication).

agnosed as not having ADD as children had normal voltages of the P300 wave; however, the late components of their ERPs (Fig. 4) appear to be asymmetrical. The significance of this latter finding is not clear. However, the fact that the two hemispheres do not, in these subjects, participate equally (by this metric) in information processing is reminiscent of McEwen's discussion of the effects of pseudosteroids in disrupting the steroid-dependent lateralization of functions in the male brain (*22*). Conceivably, this ERP measure could be reflecting the action of some teratogen (such as lead) in deranging the normal organization of areas subserving speech and cognition in these subjects.

The Measurement of Disordered Attention

In his paper in this symposium, Hoffer has referred to attention deficit as a soft-neurological sign (*9*). The difference between a soft and a hard neurological sign is that the latter may be more easily related to demonstrable lesions of the central nervous system. In the last several years we have attempted in our laboratory to relate disorders of attention, such as are manifest in ADD, petit mal epilepsy, and schizophrenia, to specific lesions or other focal disturbances of central nervous system function. I will present here some of the thinking behind this approach, and some of the preliminary results of an effort to develop a more systematic and rational analysis of disturbed attentional function. Some of this material, in a slightly different form, appears in a discussion of behavioral effects of petit mal epilepsy (*23*).

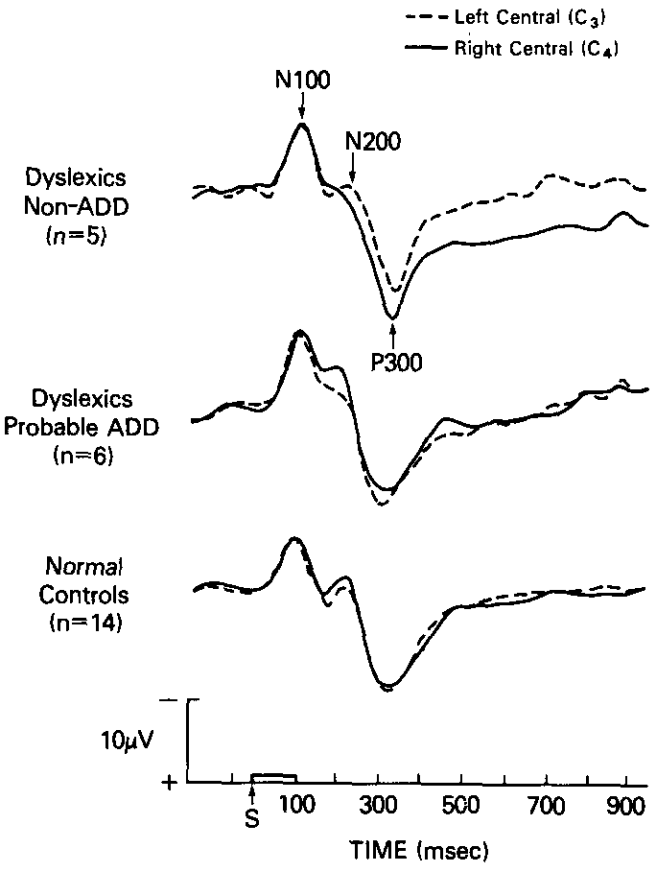

FIGURE 4. Auditory ERPs from left and right central (C3 and C4) placements from the same subjects in the investigation referred to in Fig. 3. The non-ADD dyslexic group shows asymmetric late components with reduced negativity in the right, as compared with the left central location (from Duncan, personal communication).

The Elements of Attention

In recent years cognitive psychologists have become interested in the problem of attention, and insightful and original analyses have been contributed by Kahneman (*24*), Posner (*25*), Shiffrin and Schneider (*26*), and others. A useful review of many of these contributions, in the context of the problem of attention loss in schizophrenia, has been provided by Nuechterlein and Dawson (*27*). Other earlier works on attention, edited by Evans and Mulholland (*28*) and by Mostofsky (*29*) are also apropos. An especially insightful discussion of the problem also from the viewpoint of attention loss in schizophrenia has been contributed by Zubin (*30*). According to Zubin's analysis, attention can be subdivided into a number of elements or aspects. These include: the capacity to focus upon or select some part of the environment; the ability to sustain or maintain that focus for an appreciable period; and the ability to shift adaptively from one aspect or element of the environment to another.

This analysis of the elements of attention accords well with some recent data obtained in the Laboratory of Psychology and Psychopathology of the National Insti-

tute of Mental Health. These data are derived from an analysis of an extensive series of neuropsychological tests (Table 1) administered to a variety of patient subjects and controls, studied either as inpatients or outpatients under a variety of research protocols. The data of most interest for this discussion involve the factor analysis of 10 test scores commonly considered to be measures of attention which were, in turn, derived from 8 frequently used tests of attention. These tests and the scores derived from each, were as follows:

- The Trail Making Test (*31*); time to complete.
- Talland Letter Cancellation Test (*32*); mean number correct.
- Digit Symbol Substitution Test (DSST) [subtest from the Wechsler Adult Intelligence Scale (WAIS) (*33*)]; number correct.
- Stroop Test (*34*); mean number of words.
- Continuous Performance Test (CPT) (*35,36*); mean number of correct responses, X and AX task combined.
- CPT; mean number of errors of commission, A and AX tasks.
- CPT; mean total reaction time for correct responses, X and AX tasks.
- Digit Span [subtest of the WAIS (*33*)]; total score forward and backward.
- Arithmetic [subtest of the WAIS (*33*)]; highest score.
- Wisconsin Card Sorting Test (WCST) (*37*); number of errors.

The Trail Making Test, part of the Halstead-Reitan neuropsychological battery, requires the subjects to connect a series of numbers in order, with pencil lines; then, the subject must alternate numbers and letters in a similar task. The Talland Letter Cancellation Test requires the subject to cross out designated letters in a sheet of random letters. In the DSST the subject is asked to write symbols below a series of digits in accordance with a digit-symbol code. The key feature of the Stroop Test is the requirement that subjects read a series of color names (red, green, blue) printed in inks of contrasting colors. Their scores on simpler tasks (reading color names printed in black, reading color names of color patches) are also obtained.

The CPT is essentially a visual vigilance task in which subjects are required, for periods of 10 min at a time, to press a response key for certain target letters and to withhold responses to nontarget letters. X is the target letter in the "X" task and X following A in the "AX" task. Letters appear at 1 sec intervals with a stimulus duration of 0.2 sec; targets are 25% of the stimuli in the X task and 20% in the AX task. The Digit Span and Arithmetic tests require the ability to hold numbers in short-term memory, and either to repeat them immediately (Digit Span) or to solve a verbally presented mathematical problem. The WCST requires subjects to sort a set of test cards according to a set of sample cards. The test cards present stimulus material differing in color, form, or number, which usually do not match the sample cards, and thus require some decision as to the category which defines the match. The correct sorting category is systematically changed by the examiner after the subject has made a series of 10 correct sorts in a row.

The scores obtained by a group of 86 subjects (who were also examined with a more extensive battery of neuropsychological tests) were subjected to a factor analysis and to an orthogonal rotation. The results of this factor analysis (which will be reported in detail elsewhere) indicated that the 10 scores described above could best be characterized by a series of four factors. These factors accounted for 71% of the variance on these tests.

Table 2 presents the rotated factor weightings derived from this factor analysis, together with a tentative identification of the component of attention represented by each of the factors. In four tests, Trail Making, Talland Letter Cancellation, DSST, and Stroop, factor 1 appears to be heavily weighted; All tests appear to tap some aspect of perceptual-motor speed and could be designated as measuring the focusing aspect of attention. Since speed is in fact a key feature of performance on these tests, the execute component of the task seems intertwined with focus in this factor. The CPT measures alone appear in factor 2, which can virtually unambiguously be designated a vigilance factor; therefore, it seems reasonable to label this as reflecting the sustain component of attention. Factor 3 is represented only by the Digit Span and Arithmetic tests. It seems clearly to assess a numerical-mnemonic quality of attention, and the encode aspect of attention/information processing seems to capture this. Finally, factor 4 is represented by only one test, the WCST. As in the case of factor 2, the identity of this factor seems readily apparent; it taps the flexibility aspect of attention—the capacity to shift. The same data are presented in rearranged fashion in Table 3, which identifies the factors and relates them to their presumed identity as a component of attention.

The Localization of the Elements of Attention

This discussion now turns to another related area, in order to be able to incorporate these behavioral findings into a neuropsychological/neuroanatomical context. In Figure 5 are presented a series of semischematic views of the human brain, designed to both illustrate and summarize those regions of the cerebrum that current research has implicated in one way or another as being involved in attention. Beginning with the most rostral depiction, at the lower right, are represented the tectum and the mesopontine regions of the reticular formation. Since the pioneering work of Moruzzi and Magoun (*38*) and Lindsley and colleagues (*39*), these areas have been firmly established as related to consciousness and attention. The mesial view of the right hemisphere (center of the figure) depicts the midline thalamic region (and the reticular nuclei), for which a role in attention

Table 2. Factor analytic study of attention measures.[a]

Measure	Rotated factor loadings			
	Factor 1	Factor 2	Factor 3	Factor 4
Trail Making Test	−0.797	0	0	0
Talland Letter Cancellation	0.754	0	0	0
Digit Symbol Substitution Test	0.726	0	0	0
Stroop Test	0.678	0	0	0
CPT, omission errors	0	−0.881	0	0
CPT, commission errors	0	0.877	0	0
CPT, response time	0	0.651	0	0
Digit Span	0	0	0.835	0
Arithmetic	0	0	0.719	0
Wisconsin Card Sort errors	0	0	0	0.826
Variance explained	24%	21%	14%	12%
Identity of factor	Perceptual-motor speed	Vigilance	Numerical-mnemonic	Flexibility
Component of attention	Focus, execute	Sustain	Encode	Shift

[a]Ten measures, eighty-six subjects.

Table 3. Factor analysis of attention measures.

Factor	Major loadings	Variance explained	Identity of factor
1	Trail Making Test Talland Letter Cancellation Digit Symbol Substitution Test Stroop Test	24%	Perceptual-motor speed
2	CPT, omission errors CPT, commission errors CPT, response time	21%	Vigilance
3	Digit Span Arithmetic	14%	Numerical-mnemonic
4	Wisconsin Card Sort	12%	Flexibility

[a]1 = focus, execute; 2 = sustain; 3 = encode; 4 = shift.

is supported by the work of Ajmone Marsan (*40*) and by Jasper and co-workers (*41*). In phantom on this brain view are presented the corpus striatum and hippocampus, as well as those portions of the medial frontal lobe heavily concerned with attention, including the anterior cingulate gyrus (*42*). The corpus striatum has recently been implicated in the neglect phenomenon (*42,43*). The involvement of the hippocampus in attention is supported by both behavioral and by electrophysiological measures; the classical hippocampal theta rhythm index of arousal has been well described (*44*). Both Altman (*8*) and Hoffer (*9*) have noted in discussion of their respective models that lead can deplete microneurons in the hippocampus (Altman) or decrease the growth of hippocampal tissue in an ocular explant (Hoffer). These models could account for the effects of lead on hippocampal tissue and a possible effect, therefore, on attention. The top two views provide a rough and tentative summary of current knowledge of cortical areas implicated in attention: the prefrontal cortex (*45*) and the inferior parietal lobe, lesions of which may lead to the neglect phenomenon. The inferior parietal lobule is shown of greater size in the right hemisphere view because of the reported greater likelihood of neglect following right-sided lesions (*42*). Hoffer presented data on the deleterious effects of lead on parietal cortical tissue in his ocular explant. The role of the superior temporal cortex (or, more accurately, the superior temporal sulcus) as a multimodal sensory convergence area with a presumptive role in attention is perhaps best supported by the anatomical studies of Pandya and colleagues (*46*).

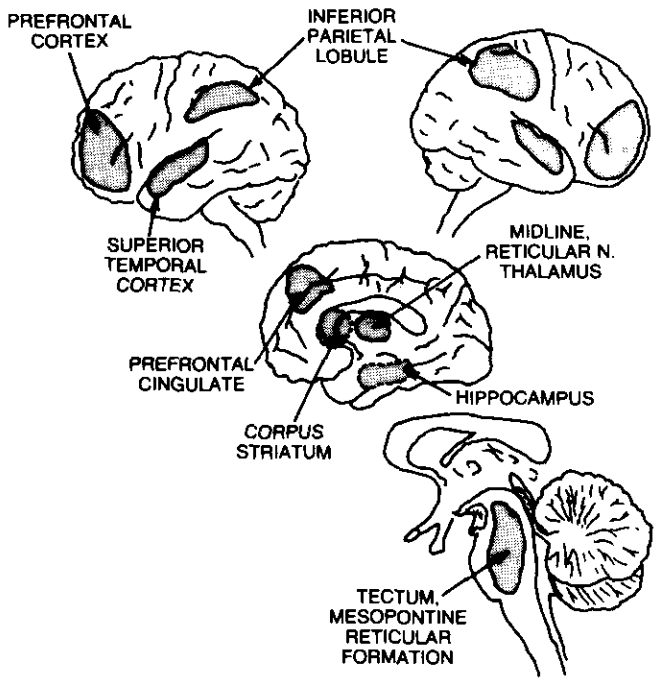

FIGURE 5. Semi-schematic representation of brain regions involved in attention.

There is little doubt that the brain structures that have been presented in Figure 5 could be construed to form a system; anatomical connections among the various areas have been described and are represented schematically in Figure 6. These pathways have been well described [e.g., Jones and Peters (*47*)] and will not be documented further here; they will be presented,

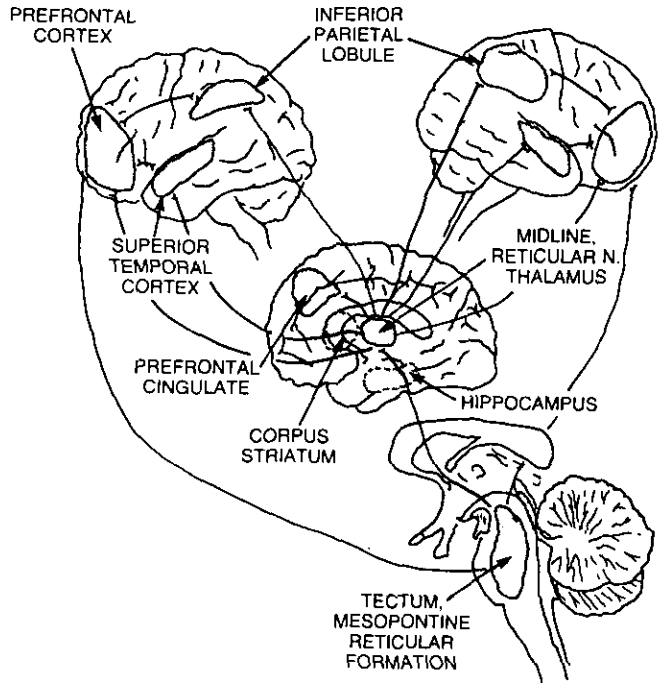

FIGURE 6. Semi-schematic representation of brain regions involved in attention; some interconnections among the regions are shown; the connections are conceivably sufficient to support the concept of an attention system.

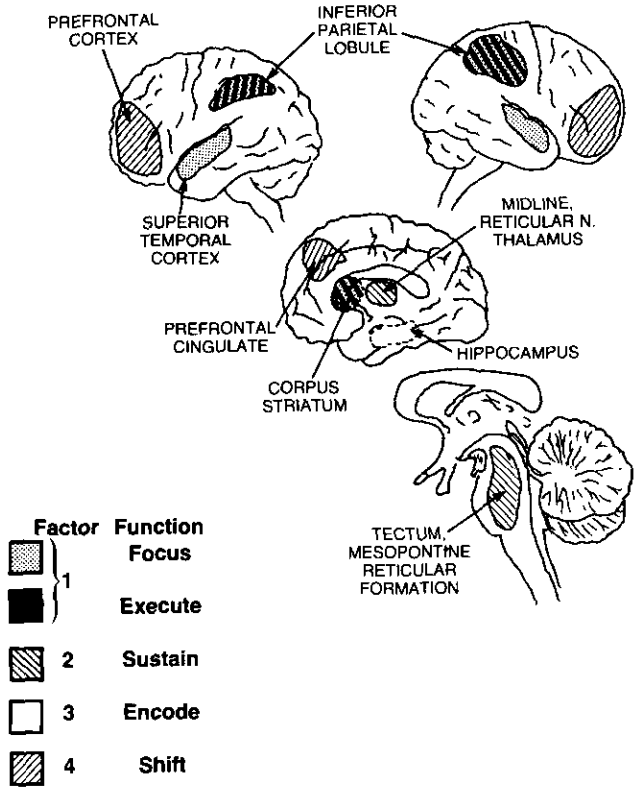

FIGURE 7. Semi-schematic representation of brain regions involved in attention, with tentative assignment of functional specializations to the regions.

however, in a more complete exposition of these ideas in a later publication. Finally, the question arises as to whether there can be a tentative assignment of the attention functions described in Table 2 (derived in part from Zubin) to the attention system components depicted in Figure 5. Since the bulk of evidence indicates that the components of attention are not equally represented throughout the brain regions, shown in Figure 5,* such an assignment can be attempted. This is illustrated in Figure 7, which is an effort to combine these two sources of information: the neuroanatomical-neurophysiological and the behavioral-neuropsychological (with special emphasis on the data of Tables 2 and 3).

It should be noted at the outset that this effort of assigning functional specialization of components of attention to differing brain regions is preliminary and is not meant to be absolute; the possibility exists, moreover, that some brain regions may share more than one attentional function. Caveats aside, what is suggested by the model is summarized in the following paragraphs.

Attention can be subdivided into a number of separate functions including focus, execute, sustain, and shift. These functions are supported by different brain regions, which are (or have become) specialized for this purpose, but which nevertheless are organized into a system. The attention system is so widespread within the brain that it is quite vulnerable, which accords well with the data that disordered attention is a common sequela of cerebral dysfunction. Damage or dysfunction in one of these brain regions can lead to circumscribed or specific deficits in a particular attention function.

The functions of focusing on environmental events are shared by superior temporal and inferior parietal cortices, as well as by structures that comprise the corpus striatum, including caudate, putamen and globus pallidus. The inferior parietal and corpus striatal regions have a strong motor execute function.

Considerable amounts of encoding of stimuli are accomplished by the hippocampus, an essential mnemonic function that seems to be required for some aspects of attention. The capacity to shift from one salient aspect of the environment to another is supported by the prefrontal cortex. Sustaining a focus on some environmental event is the major responsibility of rostral structures, including the tectum, mesopontine reticular formation and midline, and reticular thalamic nuclei.

Implications for Study of Environmental Toxins

These considerations suggest that attention is a complex and multifactorial behavior and that a more complete and ultimately, more profitable assessment of dis-

*For example, CPT deficit is not associated with frontal or temporal lobe dysfunction or lesions, but seems to be associated with brain stem pathophysiological processes (*49,50*). By contrast, WCST impairment is seen after frontal lobe, but not after temporal lobe lesions (*45*).

ordered attention requires a battery of procedures that can be related to some scheme of central nervous system localization. Some of the variability in the outcome of the lead behavioral toxicity studies reviewed by Needleman and Bellinger (*48*) could reflect variability in the measurements used to assess the behavior. Some behavioral assays of attention may be less sensitive to the effects of some toxic agents than others, and the key to the differential sensitivity may ultimately be understood in terms of a framework such as the one presented in this paper.

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