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ATTENTION DYSFUNCTION IN AUTISM: PSYCHOPHYSIOLOGICAL AND NEUROCHEMICAL PERSPECTIVES

Digby Stephen Ormond Brown

A Dissertation Submitted to the Faculty of Arts,
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ABSTRACT

ATTENTION DYSFUNCTION IN AUTISM: PSYCHOPHYSIOLOGICAL AND NEUROCHEMICAL PERSPECTIVES

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Evoked cardiac responses (ECR) and urinary catecholamine concentrations, both putative indices of attention, were examined in 36 autistics, who were diagnosed using DSM III (APA, 1980) and the Childhood Autism Rating Scale (Schopler et al., 1980, 1985). Controls were normal sex and age matched children ranging from 4 to 14 years.

Urine samples were assayed by high performance liquid chromatography. Homovanillic acid (HVA) levels were significantly elevated ($p < .01$), as was dopamine (DA) turnover, as indicated by a lower ratio of DA/HVA ($p < .01$). Noradrenaline (NA) turnover was decreased, as evidenced by higher NA/3-methoxy-4-hydroxyphenylglycol (MHPG) levels ($p < .05$). The ratio of HVA to total catecholamine synthesis was increased in autism ($p < .01$).

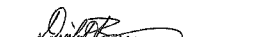
The ECR of the autistics showed a highly deviant pattern ($p < .01$), indicating a failure to orient to novel auditory stimuli, whereas the normal children showed orienting

responses (OR) and habituation with stimulus repetition.

The results are discussed in terms of the role catecholamines play in attention. It was concluded that cognitive style in autism may be characterized by information redundancy, and that this may centre on mesolimbic and mesocortical DA systems and the basal ganglia.

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Arts in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.



Nineteenth day of May, 1988.

To my wife,
Enikö Maria
and my stepdaughters
Nina and Julie

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LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
6-OHDA	6-hydroxydopamine
ADD	attention deficit disorder
ADDH	attention deficit disorder (hyperactivity)
ASCII	American Standard Code for Information Interchange
BAEP	brainstem auditory evoked response
BPM	beats per minute
BSTT	brainstem transmission time
CARS	Childhood Autism Rating Scale
CNS	central nervous system
COMT	catechol-O-methyltransferase
CSF	cerebrospinal fluid
DA	dopamine
DBP	diastolic blood pressure
DOMA	3,4-dihydroxymandelic acid
DOPA	dihydroxyphenylalanine
DOPAC	3,4-dihydroxyphenylacetic acid
DOPEG	3,4-dihydroxyphenylglycol
DR	defence response
DBH	dopamine-β-hydroxylase
ECG	electrocardiogram
ECR	evoked cardiac response
EDTA	ethylene diamine tetraacetic acid
EEG	electroencephalogram

ERP	evoked response potential
HPLC	high performance liquid chromatography
HPLC-ED	high performance liquid chromatography (electrochemical detection)
HR	heart rate
HVA	homovanillic acid
IBI	interbeat interval
IQ	intelligence quotient
L-DOPA	levo-dihydroxyphenylalanine
LTM	long term memory
MAO	*monoamine oxidase*
MHPG	3-methoxy-4-hydroxyphenylglycol
MTA	3-methoxytyramine
NA	noradrenaline
NM	normetanephrine
OR	orienting response
PBF	peripheral blood flow
PPAR	peripheral pulse amplitude response
PVR	peripheral vascular resistance
SBP	systolic blood pressure
STM	short term memory
TCA	trichloracetic acid
VMA	vanillylmandelic acid
VMT	ventral tegmental area

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Is it possible to identify the neurochemical basis of attention dysfunction in autism? This question forms the central theme of this project, and brings together a range of scientific enquiry in biochemistry, psychophysiology and autism.

Autism is a relatively recent entry in psychiatric nosology, having first been described in 1943 by Leo Kanner. Many of the issues that pertain to the development of a psychiatric classification, are still germane to autism. In particular, these include (1) characterizing the nature of the basic deficit of the syndrome, and (2) the identification of the cause of the syndrome (Maurer, 1986; Rutter and Schopler, 1987).

Although it is considered good form to identify the nature of the basic deficit of a syndrome in terms of its cause, such precise characterization is not always possible. It fails when the cause is unknown, or when multiple etiologies are possible. This applies to autism. As Ornitz (1987) observed:

> The uniqueness of this syndrome [autism] suggests one underlying pathophysiologic mechanism, although multiple etiologies that could activate or replicate such a mechanism have been demonstrated. (Ornitz, 1987, p. 148)

As our understanding of autism has advanced, so our conception of the nature of the basic deficit in autism has

changed. Early views on autism saw the basic deficit as a disturbance of affect (e.g. Bettelheim, 1967), however experimental evidence did not verify these theories. As a result there has been a shift towards conceptualizing the basic deficit in neuropsychological terms (e.g. Ornitz, 1983).

This change in approach recognizes that while the cause of autism is likely to be found at a neurophysiological level, any account of the basic deficit must be formulated in such a way that it accounts for the social, cognitive and affective deficits of the autistic.

> Whereas certainly we do not know that there is any unitary basic deficit in autism (whether defined in neuropsychological, neurophysiological or neuropathological terms), it is possible that there is one. Accordingly it is most important that research continue to be directed toward its possible identification. (Rutter and Schopler, 1987, p. 168)

Two broad approaches to the basic deficit in autism emerge from the literature, both of which emphasize the dysfunction of cognition in autism. On the one hand there are those theorists who see the fundamental problem in autism as involving a language deficit (e.g. Rutter, 1978; Rutter and Schopler, 1987). On the other hand those workers who see the basic deficit as centering on a deficiency of sensorimotor modulation (e.g. Ornitz, 1974, 1978, 1983).

In this project I adopted the view that the basic deficit

in autism is related to an attention dysfunction. One of the aims of the study was to examine attention in autistic children. A dysfunction of attention may account for both the language pathology views, and the sensorimotor modulation views, of the basic deficit in autism. Since attention is such a fundamental psychological process, both positions may be reducable to a dysfunction of attention. Previous studies (reviewed in later chapters) have indicated that attention is dysfunctional in autism.

Attention

The study of attention has a venerable history. William James was one of the first to deal directly with the issue of what attention is:

> Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence. (James, 1890/1950, p. 403-404)

James (1890/1950) drew an analogy between attention and the beam of a spotlight, the focus of which may be narrowed or widened. Attention is concerned with the regulation of the stream of consciousness.

James' (1890/1950) distinction between different kinds of

attention remains applicable today. Firstly, he differentiated between sensorial attention and intellectual attention. Sensorial attention was attention paid to sense objects, and intellectual attention was attention paid to ideas. Secondly, attention could be immediate or derived. Derived attention was attention that focused on an object because of some past association with that object. Immediate attention occurred when the object of interest was entirely novel, and unrelated to past experience. Thirdly, James distinguished between attention as passive, reflex, involuntary and effortless, as opposed to attention that was active and voluntary and demanded effort. Voluntar attention was always derived for James.

Despite its American roots, attention was not to become a key notion in American psychology until the rise of cognitive psychology. It was in the Soviet Union that the idea of attention was elaborated. This development began with Pavlov's (1927, 1928) work into reflexes.

Pavlov (1927, 1928) saw the reflex as the basic psychic act. For Pavlov the reflex was not limited to unconscious reactions, as it was for James (1890/1950). Any behaviour, *whether conscious or unconscious*, was the result of reflex activity.

Pavlov's (1927, 1928) work represented an attempt to describe all the reflexes. Pavlov believed that the strength of a reflex was an index of the strength of the nervous

system. He believed that people could be characterized according to the strength of their nervous systems, and this idea led to the development of Pavlov's typology (Gray, 1964). Pavlov saw all higher nervous system activity as the result of the superimposition of simple reflexes. His typology categorized people into different personality types, on the basis of the patterns of their reflex responses.

Pavlov (1927, 1928) distinguished between two major reflexes involved in attention. Of the first he said:

> I call it the 'What is it?' reflex. It is a reflex which brings about the immediate response in man and animals to the slightest changes in the world around them. So that they immediately orientate their appropriate receptor organ in accordance with the perceptible quality in the agent bringing about the change, making full investigation of it. The biological significance of this reflex is obvious. (Pavlov, 1927, p. 12)

This reflex is similar to James' (1890/1950) description of "passive immediate sensorial attention":

> the stimulus is a sense-impression,... it makes no difference what its nature may be, whether sight, sound, smell, blow or inner pain, — or else it is an instinctive stimulus, a perception which, by reason of its nature... appeals to some one of our normal, *congenital impulses and has a directly exciting*

quality. (James, 1890, p. 416-417)

The second major reflex that Pavlov (1927, 1928) described was a 'What is to be done?' reflex. This reflex caused the organism to take some kind of action in response to stimulation. If evaluation of the stimulus indicated danger, then a defence response was evoked. This reflex was the equivalent of James' (1890/1950) active, voluntary, derived attention.

These two modes of attention have become concepts of central importance to modern psychology. They appear under a variety of names, such as *bottom up processing* and *top down* processing, or as preperception and perception, or arousal and activation, or perception and association. However they are labelled, it is the idea of a division in attention that is important.

Pavlov's (1927, 1928) work was taken up by Sokolov (1958, 1963), who described the orienting response (OR), defence response (DR) and adaptation response. Sokolov's OR was equivalent to Pavlov's 'What is it?' response. The DR identified by Sokolov was not identical to Pavlov's 'What is to be done?' response, but represented a specific instance of the more general 'What is to be done?' response.

Whereas Pavlov's (1927, 1928) description of reflexes focused on somatic components, such as head turning, Sokolov (1958, 1963) emphasized the central nervous system and autonomic nervous system changes that accompanied the

appearance of a reflex, such as changes in electroencephalogram (EEG) synchronization and blood pressure. Sokolov's pioneering work was taken up by psychophysiology, and portions of this study were in the same vein.

Attention and Selfregulation

Three major developments have influenced our understanding of attention. Firstly, the concept of arousal provided common link between work in neurophysiology and studies on the psychophysiology of attention. Brain areas involved in arousal, were important in attention too. Attention was characterized by a growing understanding of the underlying brain mechanisms (Khomskaia, 1972/1982).

Secondly, with the rise of cognitive psychology and the information processing revolution, attention was transformed from vague blanket term, to one with specific meanings. The role of attention in information processing began to be understood, and mechanisms which controlled information flow were delineated. Concepts central to attention, such as habituation, which can be traced back to Pavlov (1927, 1928), were given precise definitions by information theory. Attention came of age.

Thirdly, and much more recently, advances in biochemistry have meant that the neurochemical basis of attention has begun to be explored.

Current theories of attention reflect these three developments (McGuiness and Pribram, 1980; Tucker and Williamson, 1984). The ideas postulated in these theories played a central role in this project. These theories linked different aspects of attention to specific neurotransmitter systems. The 'What is it?' response was described as having a noradrenergic basis, and the 'What is to be done?' response was believed to have a dopaminergic underpinning. Evidence (reviewed in later chapters) suggests neurotransmitter pathology in autistics.

According to these theories, distinct modes of information processing characterize the 'What is it?' and 'What is to be done?' responses. The 'What is it?' response has been speculated to be under the control of a habituation biased processing mechanism (Tucker and Williamson, 1984). Under these circumstances the locus of control in attention is external. The locus of control in attention is internal when information processing is modulated by a redundancy bias.

As environmental demands change, so the locus of control in attention shifts between internal and external sources. Differences between individuals suggest that some people may rely more on one mode of information processing control of attention, than another mode. Selfregulation of attention varies between people. This kind of difference in 'cognitive style' between individuals parallels the distinctions that Pavlov (1927, 1928) attempted to draw between people in terms

of their differences in reflex responses.

This kind of thinking dovetails with developments in psychiatry, where different personality types are believed to have characteristic differences in their neurochemical makeup (Crow, Johnstone, Longden and Owen, 1978; Julien, 1981; Swerdlow and Koob, 1987).

Goals of the Study

This project attempted to shed some light on the basic deficit in autism by examining attention in a group of autistic children. An evoked cardiac response (ECR) paradigm was used. This experimental paradigm provided data about information processing in the attention mechanisms of autistics. This data was interpreted in terms of concepts developed in psychophysiology, particularly the ideas of habituation and redundancy biases, and internal and external loci of control.

The basic deficit in autism was examined in another way by assaying urine samples from the children. This provided information about their neurochemical status.

Finally, an attempt was made to understand the relationship between the psychophysiological data and the neurochemical data, in terms of current models of the neurochemistry of attention.

CHAPTER TWO -- CURRENT PSYCHOPHYSIOLOGICAL ISSUES IN ATTENTION

The comparison of measures of attention obtained from a normal group and a clinical group, presumes that attention in the normal group can be theoretically modelled in some fashion. Such comparisons assume that we know what attention is, and how it can be measured, and this knowledge supplies the basis on which comparisons between normal and other groups may be made in terms of the operation of attention.

It is reasonable to make these assumptions. If they were not made, clinical groups would never be studied, because research effort would be expended on developing and refining theories of attention, and not on examining attention in clinical populations. Making assumptions is acceptable, provided problems associated with the assumed theories are not overlooked. My intention in this chapter is not to discuss theories of attention. That is beyond the scope of this project. What is important in this chapter is to specify the problems currently associated with traditional interpretations of attention, and of evoked cardiac responses.

Attempts at the resolution of these problems have been partially responsible for the development of influential approaches to attention. These more recent models form the theoretical underpinning to attention in this study, and they are briefly discussed in this chapter.

In this study attention was measured using evoked cardiac

responses to auditory stimuli. The interpretation of the results depends directly on the significance attached to cardiac deceleration in response to stimulation. This is an issue that has been the focus of a considerable amount of debate in psychophysiological theorizing.

The 'Cardiac Deceleration as a Sensory Process' Assumption

An issue of considerable importance in cardiovascular psychophysiology has been whether evoked cardiac responses are functionally related to a sensory process, or to a motor process. Views which hold that attention can be measured by evoked cardiac changes, assume that an ECR reflects the operation of a sensory process, rather than a motor process. An important rival to this view was the model proposed by Obrist (Obrist, Howard, Lawler, Galosy, Meyers and Gaebelein, 1974; Obrist, Langer, Grignolo, Light and McCubbin, 1980).

On this model changes in cardiovascular output were seen as relating to metabolic demands. In particular, evoked cardiac deceleration was taken as an index of somatic quieting, prior to the execution of some action. For Obrist et al. (1974, 1980) the function of cardiac deceleration was related to priming of the musculature, and anticipated metabolic demands. This reduction in muscle tone was seen as related to attention only in so far as it might assist in information processing by reducing the 'noise' associated with

movement. Conversely, cardiac acceleration was associated with the execution of a given behaviour. On this view cardiac responses were not directly related to attention, and indexed metabolic demands, and not information processing demands.

Specifically, Obrist et al. (1980) predicted that during orienting, cardiac deceleration would be accompanied by a cessation of motor activity. The Obrist model (Obrist et al., 1974, 1980) has existed alongside models which see the ECR as indexing attention. Recently, Siegel, Savanes, Gaddy and Campbell (1987) recently showed that deceleration during orienting was not accompanied by somatomotor quieting, as demanded by Obrist model. The results of this experiment provided support for models linking the ECR and attention, and refuted some predictions made by Obrist et al. (1974, 1980). Siegel et al. concluded that cardiac deceleration was an index of sensory information processing. Their result lends credence to the assumption made in this research project that attention may be measured by the ECR.

Problems with Traditional Interpretations of Attention

For the last 20 years evoked cardiac responses have been widely accepted as indices of the orienting response and the defence response (Coles, 1983; Davies, 1983; Graham, 1979, 1982; Porges, 1984; Siddle, Kuiack and Stenfert Kroese, 1983; Velden and Schumacher, 1979). This theoretical position may

be traced back to a seminal article by Graham and Clifton (1966), in which they linked the work by Sokolov (1958, 1963) to that of Lacey and Lacey (Lacey, B.C. and Lacey, J.I., 1980; Lacey, J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974;).

Sokolov (1958, 1963) had been working on the orienting, defence and adaptation responses. His work was largely an extension and refinement of the ideas of Pavlov (1927, 1928). Sokolov had identified some of the physiological components of these reflex responses. He also developed an influential account of attention to explain his results, which utilized the concept of a mismatch between a hypothesized neuronal model of a stimulus and the stimulus itself, an idea originating in Gestalt psychology. Sokolov's work exemplifies traditional approaches to the orienting and defence responses.

The Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974) had been researching the relationship between cardiac acceleration and deceleration, on the one hand, and the rejection and intake of stimuli, on the other. The Laceys noted that tasks which required the intake of stimuli, were accompanied by cardiac deceleration, whereas acceleratory responses were observed under conditions where the rejection of sensory stimulation was demanded. They concluded that the functional significance of cardiac deceleration was linked to the intake of stimuli.

Graham and Clifton (1966) argued that the cardiac deceleration and concomitant sensory intake described by

the Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974) was equivalent to the orienting response, identified by Sokolov (1958, 1963). As a corollary to this, Graham and Clifton postulated that cardiac acceleration was associated with Sokolov's defence reflex. On the basis of the Graham and Clifton model it followed that cardiac deceleration was an index of the orienting reflex, and increased heart rate an index of the defence response.

Although the Graham and Clifton (1966) model is satisfying in its symmetry, and in the links it draws between divergent theories, it now appears that it, and portions of Sokolov's (1958, 1963) views are incorrect. Anomalies between theory and experimental results pose difficulties for the interpretation of the psychophysiological data obtained in this study, in terms of the aforementioned theories.

What are these problems with traditional interpretations? Barry (1986) has argued powerfully against the Graham and Clifton (1966) model. According to Sokolov's (1958, 1963) position, the magnitude of an orienting response (OR) is directly proportional to the intensity of the stimulus. However, on the basis of earlier studies of his own (Barry, 1977, cited in Barry, 1986) and by the re-analysis of ECR data supplied by other psychophysiologists, Barry (1986) showed that the magnitude of the ECR was not in a linear relationship with the intensity of the stimuli, as predicted by Sokolov,

but instead displayed an inverted "U" shape.

Barry (1986) also argued that the ECR does not reliably show the habituation effects for trials that is predicted by Sokolov's (1958, 1963) theory of orienting. His argument for the nonhabituation of the ECR is weaker than his argument for the failure to find the predicted stimulus intensity - response magnitude effects in the ECR. A substantial portion of Barry's agrument that the ECR does not show habituation effects, depends on methodological issues which are not germane to the problem, such as whether peripheral pulse is a better measure of cardiac activity than the electrocardiogram. Furthermore, graphs of Barry's own data do show habituation effects, contrary to his claims of the nonhabituation of the ECR.

Barry (1986) argued that the Graham and Clifton (1966) model was incorrect because cardiac deceleration does not show the intensity/magnitude and habituation effects demanded by Sokolov's (1958, 1963) theory of the OR. This portion of Barry's argument rests on problems with Sokolov's theory, and not directly with Graham and Clifton's account.

A more powerful argument against the Graham and Clifton (1966) model is as follows. The threshold at which a stimulus begins to evoke an acceleratory cardiac response, rather than a decelerator response, should correspond to the threshold between the orienting and the defence responses, according to the Graham and Clifton account. However, Barry (1986)

examined his own data, as well as the data on which Graham and Clifton based their thesis, and found that this threshold effect could be observed at stimulus intensities of as low as 40 dB. Sokolov (1963) postulated that the prepain threshold was at 65 dB. Thus at these *stimulus intensities no defence* response should be observed. Yet application of the Graham *and Clifton model results* in the absurd claim that an acceleratory cardiac response to a stimulus of such moderate intensity is a defence response.

Given these problems with the Graham and Clifton (1966) model, it would be invalid to interpret the cardiac data obtained from this experiment in terms of their model. As is apparent from the psychophysiological literature, the model of orienting proposed by Sokolov (1958, 1963) is extremely influential. It is noteworthy therefore, that this model has its share of problems, too.

According to Sokolov (1958, 1963) the OR should be elicited when a stimulus does not appear *when expected to* appear. This has been termed the "missing stimulus effect", and *follows from the criterion for orienting* that any change in the properties of the stimulus should result in re-elicitation (dishabituation) of the OR. However, experimental support for the missing stimulus effect has ranged from equivocal to decidedly weak.

Barry (1986) found that missing stimuli evoked a skin conductance orienting response in only 50% of subjects.

Siddle, Remington, Kuiack and Haines (1983) used a paired stimulus paradigm to examine the missing stimulus effect. They found that when one element of the stimulus pair was omitted, dishabituation was observed in only 42% of subjects. This increased to 83% when the intensity of the stimulus was changed from 65 dB to 105 dB. However, stimuli in the 105 dB range are known to elicit defence responses, rather than orienting responses (Graham, 1979; Turpin, 1986), and this makes the figure of 83% difficult to interpret.

Convincing evidence that Sokolov's (1958, 1963) predictions are not met by the omission of expected stimuli comes from the only study to date done on the missing stimulus effect in animals (Foreman and Thinus-Blanc, 1987). They found that 15.4% of omitted stimuli produced orienting, as opposed to 53.3% of stimuli which appeared unexpectedly. Thus the unexpected appearance of a stimulus evokes an OR more reliably that its unexpected omission. For Sokolov there should be no difference between these two responses.

These disconfirmatory results are important because according to Sokolov's (1958, 1963) theory, dishabituation to a missing stimulus occurs because of the operation of a stimulus comparator mechanism which detects a mismatch between the neuronal model of the stimulus, and the missing stimulus. For the same reasons, the appearance of a stimulus where it is unexpected, should result in an orienting response. The failure to confirm the missing stimulus effect, and the

finding that missing stimuli elicit fewer ORs than unexpected stimuli, suggests that either the stimulus comparator mechanism is not correct as theorized by Sokolov, or that dishabituation to missing stimuli is not definitive of the orienting response.

A recent study (Biddle, 1985) examined this issue from the point of view of the missing stimulus effect, and concluded that comparator theories of orienting were sound. It follows that the problem lies with Sokolov's (1958, 1963) criteria for orienting. Nevertheless, Sokolov's theory has many redeeming features, and it seems excessive to discard the entire theory because one of the criteria for orienting has been shown to be incorrect. Theories of orienting, such as those due to Pribram and McGuiness (1975) and Ohman (1979), which take the important features of Sokolov's work, and build on them to create more exacting accounts of the orienting response are appealing. It was therefore with reference to theories such as these that the cardiac data obtained in this study was interpreted.

Current Conceptions of the Evoked Cardiac Response

Given the problems associated with the Graham and Clifton (1966) hypothesis, the partial refutation of Sokolov's (1958, 1963) theory of orienting by the missing stimulus effect, and the demise of the cardiac somatomotor hypothesis (Obrist et

al., 1974, 1980), none of these traditional views may be used as the theoretical basis for the interpretation of the experimental results obtained in this study.

The ECR may be explained either by reference to models which deal exclusively with the ECR, or by models of the orienting response that describe the ECR as an index of orienting. *The former is exemplified* by the intake/rejection hypothesis of the Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974), and the latter by accounts of *orienting such as those* by Pribram and McGuiness (1975) and Ohman (1979).

The model of the ECR described by the Laceys is important because it emphasizes how different environmental *demands* require different kinds of information processing in attention. The notion of different kinds of information processing is pivotal to this study. It implies the idea of '*cognitive style*'.

One of the aims of this study was to examine how cognitive attention style differed between normal and autistic children. We may *distinguish between phasic* changes in attention which are related to environmental demands, and tonic changes of attention which are related to cognitive style. Given that cognition *is dysfunctional in autism* (Goldstein and Lancy, 1984; Sigman, Ungerer, Mundy and Sherman, 1987), phasic changes in their attention, as measured by the ECR, occur against a background characterized *by* a

certain cognitive style. The nature of phasic changes in attention may provide an insight into the nature of tonic attention related processes. Cognitive style in autistics may be illuminated by their ECR.

The model of the Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. & Lacey, B.C., 1970, 1974) suggests that cognitive style may also be described in terms of intake and rejection. Autistics may have a cognitive style characterized by the augmenting of stimuli; they may be hyperresponsive. Alternatively autistics may tend to reduce stimulation; they may be hyporesponsive.

This approach to cognitive style is limited, and relates to only one dimension of attention: the degree to which information processing is facilitated. It says nothing else about how information is processed. Other important components to information processing and cognitive style, are indexed by orienting behaviour. These include dimensions such as arousal and habituation. When seen from a higher level perspective, cognitive style is part of the pattern of selfregulation used by a person. The ability of the autistic to selfregulate may be impaired.

Pribram (Pribram, 1980a, 1980b, 1981; Pribram and McGuiness, 1975; McGuiness and Pribram, 1980) proposed a model of attention that consisted of three components: arousal, activation and effort. Arousal and activation were seen as involuntary processes, which, in response to situational

demands, controlled the intake and rejection of information, respectively. Arousal was linked to the orienting response, or Pavlov's (1927, 1928) 'What is it?' response, and activation to motor readiness, or Pavlov's 'What is to be done?' response.

Pribram and McGuiness (1975) and McGuiness and Pribram (1980) followed Graham and Clifton (1966) by linking cardiac deceleration to orienting. However, their view of the orienting response was not equivalent to Sokolov's (1958, 1963) *position* (Spinks, Blowers and Shek, 1985; Spinks and Siddle, 1985). Nor did Pribram see cardiac acceleration as an index of the defence response, but rather as an index of activation and motor readiness. Therefore the criticisms leveled at Graham and Clifton do not apply to Pribram's *linkage of cardiac deceleration to orienting*. The Pribram model is also important because it links attention to anatomy and physiology. This will be discussed in more detail in later chapters.

The model of Pribram and McGuiness (1975) and McGuiness and Pribram (1980) has been extended by Tucker and Williamson (1984), who introduced the concepts of a "habituation bias" and a "redundancy bias" into their model, to explain selfregulatory controls on attention. One of the important aspects of the work by the Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974) was that it emphasized the importance of

selfregulation in attention (Velden and Schumacher, 1979). The intake or rejection of stimulation is a consequence of the information processing demands made on the organism by environmental circumstances. The organism must selfregulate the flow of information in order to allocate processing resources with maximal efficiency and respond optimally to prevailing environmental circumstances (Carver and Scheier, 1981; Scheier and Carver, 1982).

Selfregulation and attention are closely linked, and may be indistinguishable from the point of view of information processing and control theory (Carver and Scheier, 1981; Scheier and Carver, 1982). The efficiency of attention is threatened by perceptual overload or response incoherence (Kahneman and Triesman, 1984). Perceptual overload occurs when the mechanisms which regulate responsivity to input fail, and the organism is flooded with novel stimuli. Response incoherence occurs when the order of a sensory or motor response set fractures, and, for instance, panic ensues.

Normally, orienting is followed by habituation. The habituation bias inhibits further processing if the information in a given stimulus is identical to a previous stimulus, and is not otherwise significant. Thus, if there is no change in the information content of the input, further processing is attenuated, and the response of the organism to the stimulus diminishes over time.

On the Tucker and Williamson (1984) model, the process of

arousal operates by applying a habituation *bias to incoming stimuli*. The effect of this bias is to prime the organism for novel input, and prevent perceptual overload by gating out stimuli that have already been processed, and carry no new information (Pribram, 1980; Tucker and *Williamson*, 1984; Wickens, 1984).

The other process available to an organism which must selfregulate its attention is the redundancy bias, mentioned above. Redundancy regulates *information flow* by restricting the class of stimuli that may receive further processing. If a signal is not a member of the criterion class, it is considered redundant, and its subsequent processing is inhibited. As the activation *redundancy* bias takes control of attention, the amount of information processed becomes restricted. The rate of information turnover under a redundancy bias is low, whereas a habituation bias results *in* a faster rate of *information* turnover.

Spinks et al. (1985) consider one of the most influential contemporary models of the orienting response to be Ohman's (1979). For Ohman the deceleratory ECR of the normal *children represents* a *preattentive* call for processing space in the limited capacity central processor, which he equated with short term memory (STM). The capacity of STM may be allocated to a single resource, or distributed (*usually unequally*) *amongst* multiple competing resources (Davies, 1983, Wickens, 1984). Ohman equates the ECR with orienting. On this view,

failure to identify a stimulus results in a mismatch between STM and long term memory (LTM). A mismatch initiates a search of LTM, which is indexed by increased heart rate on this account. The similarities with Sokolov (1958, 1963) are apparent on the Ohman model.

When an orienting response occurs and the habituation bias is operative, a parallel information flow may be used to increase processing efficiency and prevent overload (Pribram, 1980). This is possible because parallel processing limits the depth to which information is processed, and does not take up capacity in the central processor (Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977). It may thus proceed rapidly, and in parallel with ongoing central processes and other preattentive processes.

The arousal-habituation and activation-redundancy controls over attention are inversely related to each other (Tucker and Williamson, 1984). Under conditions in which arousal based habituation bias dominates, the representational scope of the organism is increased, and it is primed for the maximum number of novel inputs. The "focus" of attention is broadened. Short term memory (STM) capacity rapidly becomes saturated by information. Also, under these conditions, because redundancy of information is minimal, the restraints on information flow are few. Information turnover in STM therefore occurs rapidly, frequently and easily.

By contrast, the dominance of the activation system has

the effect of sharply delimiting the representational scope of attention. The "focus" of attention is narrowed. Information processing falls under the tight, internal control of the organism. The rate of change in the information channels is slowed. The redundancy bias primes the organism for stimuli which are currently of significance, because of prevailing environmental conditions. Stimuli are only processed if they satisfy the redundancy bias requirements.

Summary

I have shown that there are a variety of problems associated with traditional views of the orienting response (Sokolov, 1958, 1963), and its relation to evoked cardiac responses (Graham and Clifton, 1966). These problems proscribed using these traditional views as the basis for the interpretation of the experimental results.

More recent models of the orienting response (McGuiness and Pribram, 1980; Ohman, 1979; Pribram, 1980, 1981; Pribram and McGuiness, 1975; Tucker and Williamson, 1984) avoid these pitfalls. At the same time they provide some constructs that are useful in understanding the operation of attention mechanisms. These may allow for a description of the autistic's attention processes in terms of selfregulatory control processes, such as habituation and redundancy.

I now turn to a review of the literature on psychophysiological findings in autism. This literature shows that attention may be dysfunctional in autism. It also implicates certain regions of the brain in the pathophysiology of autism. Models of attention (McGuiness and Pribram, 1980; Pribram and McGuiness and Pribram, 1975; Tucker and Williamson, 1984) implicate certain brain areas in attention processes. The connections between brain areas, attention and autism will be explored in subsequent chapters.

CHAPTER THREE — PSYCHOPHYSIOLOGICAL FINDINGS IN AUTISM

In this chapter the literature on the psychophysiology of attentional functioning in autistic persons is reviewed. The chapter is divided into two major sections. In the first section the electrophysiological correlates of central nervous system (CNS) activity in autism are discussed. This section focuses on electroencephalogram (EEG) and evoked response potential findings in autism. Research on nystagmus abnormalities is also covered. In the second section, the psychophysiological correlates of autonomic nervous system activity in autism are discussed. Two major types of autonomic variables are considered; electrodermal responses (EDR) and cardiovascular responses. Some less common measures, such as respiratory period, are also reviewed, as is some unusual data from soundfilm microanalysis of autistics.

At issue in this chapter is the question of what psychophysiological studies indicate about the nature of attention in autism. If attention is indeed dysfunctional in autism, as the literature reviewed below suggests it is, then it becomes necessary to attempt to specify the precise nature of the attention deficit. A blanket term like attention conveys little information. What is required is an analysis that specifies what is dysfunctional in attention in autism. Key issues include: (1) whether information processing in

autism is augmented or reduced by stimulation, (2) whether or not arousal is normal in autism, and if not, whether autistics are hyper or hypo aroused, (3) whether the 'What is it?' component of attention, or the 'What is to be done?' component is dysfunctional, or both, and (4) how the control processes of habituation and redundancy operate in autism.

Central Nervous System Correlates of Attention in Autism

Electroencephalogram Studies. Despite the widespread agreement that autistic persons are at greater risk of EEG abnormalities, and epileptic seizures, than the normal population, no pattern in the EEG emerges that is characteristic of autism (Golden, 1987). Findings include paroxysmal spiking, increased slow wave potentials, and generalized slowing (De Meyer, Barton, De Meyer, Norton, Allen anc Steele, 1973; Golden, 1987; Ornitz, 1979).

The most influential early study on the EEG in autism was by Hutt, Hutt, Lee and Ounsted (1964). They argued that autistics were in a state of chronic hyperarousal, and reported that although the sleep EEGs of autistics were normal their waking EEG showed a marked increase in desynchronized activity, as well as low voltage irregularities, both suggestive of hyperarousal. On the basis of their data, Hutt et al. argued that the autistic

children in their study were in a state of arousal similar to the adult population, rather than showing the EEG arousal profiles characteristic of children their own age, or *younger*. This view is not consistent with the frequently advocated position that autism may be a developmental disorder (Cohen, Paul and Volkmar, 1987).

There is little agreement on the incidence of EEG abnormalities in autistics (Golden, 1987). Creak and Pampiglione (1969, cited in Golden, 1987) reported abnormal EEG's in 83% of their autistic subjects. Despite this high *incidence rate*, no type of EEG abnormality emerged that was characteristic of autism.

De Meyer et al. (1973), undertook a *major longitudinal* study which examined EEG profiles in 126 psychotic children, first at approximately 5½ years and then again at 12 years. They found that 66% of their subjects showed marked EEG abnormalities, and that 14% had epileptic seizures. The *level of brain dysfunction*, as measured by EEG and psychometric testing at the first assessment, was a poor predictor of general prognosis at the second *assessment*.

It should be noted that in the De Meyer et al. (1973) study the term "autistic" was used in a very wide sense, and covered three patient groups: early childhood schizophrenia, primary autism and secondary autism. In terms of current *diagnostic criteria (eg. American Psychiatric Association*, 1980; Schopler, Reichler and Renner, 1985) only the primary

autistic, and perhaps some of the secondary autism group, would be considered autistic. It is not clear how much the percentages reported by De Meyer et al. would change if more stringent diagnostic criteria were applied to their data.

What is the relevance of these EEG findings for autism and attention? Despite the vagueness of some of the data, it is clear that some, probably the majority, of autistics have pathological EEG profiles. Since arousal is a major component of attention, the finding (Hutt et al., 1964) that autistics seem to be hyperaroused implies that their attentional abilities may be impaired in some fashion. Other EEG data (De Meyer et al., 1973; Golden, 1987), such as spiking activity and slowing are consistent with a generalized deficit in brain function in autism, which may be related to arousal.

Precisely how a generalized dysfunction in arousal would compromise attention in autistics is not clear from the EEG studies. Hutt et al. (1964) suggested that the stereotypies characteristic of the autistic may be related to their level of sensory stimulation, which in turn is related to their level of arousal. In support of this view, they found that as environmental complexity was increased, and by implication, levels of stimulation and arousal, so did the rate of stereotypies. In terms of attention, the Hutt et al. results were indicative of a dysfunction in the motor, rather than the sensory, components of attention in autism.

Not all EEG studies have confirmed Hutt et al.'s (1964) contention that autistics are hyperaroused, however. Lelord, Laffont, Jusseaume and Stephant (1973) found no evidence for hyperarousal in autistics. Furthermore, conceptualizations of arousal have developed considerably since Hutt et al.'s research. It is now generally accepted that arousal is not a unidimensional process, but displays different characteristics depending on the attentional demands currently made on the organism (Lacey, J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970). Measures of arousal may show changes in opposite directions, in response to stimulation. To specify the nature of the attentional dysfunction in autism, more information is required than is supplied by the EEG.

The EEG is not a measure of phasic responses to stimulation, but an index of tonic brain function. It is a measure of the ongoing electrical activity of brain tissue at a given location. Such data might tell us about *general dysfunctions, but they proscribe more specific* interpretations, particularly as far as attention is concerned. The EEG data reviewed above only indicates that there is a severe disruption of the normal pattern of electrical activity in the brains of a large proportion of autistic persons. It lends support to the idea that attention is dysfunctional in autism because a generalized pathology in brain activity is likely to effect a *range of*

centrally controlled functions, including attention.

One problem of the autistics' EEG is confounded by a major methodological problem, which applies to most research on autism. Autism is associated with a variety of neurological conditions, such as epilepsy, mental retardation, childhood psychosis, and general developmental delays. Finding a difference between a normal control group and an autistic group does not mean that the difference is specific to autism. Depending on the aim of the study, and the nature of the hypothesis, it may be appropriate to use specific control groups, such as a group matched for mental age, or a psychotic group, in additional to age matched normal subjects. Adequate controls are often lacking in research on autism.

Orintz (1987) reviewed the EEG data on autism and stated:

> It can be concluded that abnormal EEGs do occur in some autistic children, reflecting the extent to which infantile autism occurs in association with various organic syndromes... and thereby broadening our appreciation of the multiple etiologic factors underlying autism. It can also be concluded that the presence of abnormal EEGs adds little to our understanding of the underlying autistic symptoms. (Ornitz, 1987, p. 150)

For that reason event related potential (ERP) recordings

have been more widely used to assess autistics. This type of data is more easily interpreted because under these conditions the stimulus is controlled, and the response is more apparent, and easily examined. The ERP experimental paradigm allows for the assessment of components of attention, such as orienting, habituation, and dishabituation, although this has not always been the intent of ERP studies.

Event Related Potential Studies. Fein, Skoff and Mirsky (1981) measured brainstem auditory evoked potentials (BAEP) in 16 autistic children, and they found bilaterally prolonged brainstem transmission time (BSTT) in 9 (56%) of them. This is consistent with the finding that the EEG of autistics is usually slowed (De Meyer et al., 1973). Fein et al. (1981) also reported that autistics were characterized by prolonged left ear stimulation latencies. By examining the relationship between the BAEP data and the concurrence of autistic symptoms, they interpreted their findings to indicate that attentional and motivational abnormalities may be more primary to autism than auditory or language disorders.

Fein et al.'s (1981) findings have been criticized by Courchesne, Courchesne, Hicks, and Lincoln (1985a) on the grounds that they did not include controls in their study. Courchesne et al. found that compared to a normal group, autistics showed no BAEP differences. They did, however,

find differences for sense modality in the autistic group (longer auditory latencies), that were not present in the normal group. Despite Courchesne et al.'s objections to the lack of controls in the Fein et al. study, other reports (discussed below) on brain stem evoked potentials in which adequate controls were included confirm the Fein et al. findings.

Highly deviant transmission times were found in 57% of autistics by Tanguay, Edwards, Buchwald, Schwafel and Allen (1982). Like Fein et al. (1981), they found that there was a difference for the lateralization of stimuli. Although Fein et al. (1981) found deviations in only the left ear, Tanguay et al. (1982) found asymmetries for both ears, although no individual autistic was deficient in both ears.

Tanguay et al.'s (1982) results are also interesting in other respects. Firstly, they used two control groups, both normal and age matched, but one was matched for sex too. They found that the number of deviations decreased (to 57%) when autistics were compared to sex matched controls. This indicates the importance of matching for sex in studies on autism.

Secondly, although they found increased transmission time for some interpeak intervals, they also found decreased transmission time for other intervals. This kind of polarization and variability of findings may be of importance. It may indicate that the deviance from normal is

not always constant in autism. Perhaps the range of values a physiological parameter may take on, is increased in autism; autism may be characterized by greater variability in physiological measures than normal. Tanguay et al.'s (1982) results showed considerable variance for lateralization, and were not skewed in favour of a particular side.

Gillberg, Rosenhall and Johansson (1983) found evidence for deviant BSTT 33% of their autistic subjects. Interestingly, none of the subjects in their psychotic control group had abnormal auditory brainstem responses. This indicates that deviant BSTTs are not a function of psychosis in general, and may be specific to autism. Like Tanguay et al. (1982), Gillberg et al. (1983) also reported an asymmetry in some of their autistic's brainstem responses, that were not present in the normal control group. On the basis of the distribution of their data they concluded that there were two subtypes of autistics: one with no brainstem abnormalities, and one with marked brainstem electrophysiological deviance.

The evidence reviewed above supports the hypothesis that there is a dysfunction in the transmission of neural impulses in the brainstem of the autistic. BSTT may be either increased or decreased, and may be asymmetrical. Some brainstem evoked response studies show that there is a peripheral defect, indicated by a delay in Peak I latencies of the auditory brainstem response (Tanguay et al., 1982).

Such a dysfunction is not directly associated with a dysfunction of attention. However, most of the brainstem evoked responses that have been reported to be abnormal *in* autistic children, *are related to neural* conductance occurring *at* least 10 msec post stimulus onset. They therefore imply a central processing deficiency, and perhaps a consequent dysfunction of attention (Qades, 1982).

Event related potentials have also been studied at the cortical level in autistics. *Lelord et* al. (1973) did an evoked *response* experiment using sound coupled to light stimuli. Their results revealed the presence of a late slow wave potential, about 700 msec after stimulus onset, that appeared in only the autistic tracings. These slow waves were rarely observed when sound was presented *alone during* the habituation *series*, and were elicited mostly by the coupling of the stimuli. The potentials evoked were more variable and irregular in the autistics than in normal controls. The amplitude of the evoked response was smaller in the autistics.

Since these slow waves *were similar* to the contingent *negative* variation, a characteristic wave of cortical depolarization that accompanies stimulation, and is associated with motor priming, expectancy and anticipation of information (Pribram and McGuiness, 1975), Lelord et al. (1973) proposed that the late *slow waves represented* a *diffuse motor component* to both the perceptual and the

associative processes in autism. Their distinction between perceptual and associative processes parallels the distinction drawn earlier between '*What is it?' responses*, and *orienting* calls for capacity in STM, on the one hand, and 'What to do?' responses, and the search of LTM, and the execution of behaviours, on the other. Note that the contingent negative variation *itself does not appear* to be *dysfunctional* in autism (Ornitz, 1987) and that the late slow waves reported by Lelord et al. (1973) occur in addition to the contingent negative variation. This association of an abnormal motor component to *perception in autistics* is similar to Hutt et al.'s (1964) linkage of stereotypies to environmental complexity.

Martineau, Laffont, Bruneau and Lelord (1980) replicated the Lelord et al. (1973) *findings* of a late slow wave potential in the autistics. They also found significant differences between the autistic and normal subjects on peaks in the 100 - 400 msec range. Martineau et al. demonstrated that the *late slow wave potentials* were either positive or negative, again indicating the variability of results obtained on autistic children. Lelord, Callaway and Muh (1982) found differences in cortical evoked potentials of autistics for both *sound and light stimuli*. Depending on the site of the electrode the latencies were either significantly longer or shorter in the autistic children. This held true for stimuli presented either alone, or as part of a *conditional stimulus*

paradigm. These transmission time abnormalities at the cortical level are consistent with the BSTT deviances discussed above (Fein et al., 1981; Tanguay et al., 1982; Gillberg et al., 1983).

The P300, a normal late auditory evoked response usually taken to indicate cognitive processing, has been the subject of a number of reports. Niwa, Ohta and Yamazaki (1983), examined four autistic children, four Down's syndrome children and five normal controls. For the condition involving no task, the autistics showed smaller amplitude of response than the other two groups. This result is consistent with Lelord et al.'s (1979) finding that evoked response amplitude is smaller in autistics. Latencies of the P300 were no different amongst all the groups. Niwa et al. (1983) interpreted their results as indicating a deficiency of the "active stimulus evaluating process" in autistics. They also argued that autistics are unable to discriminate between stimuli, because no difference in response was found between tasks. This suggests that components of attention which are related to the identification of stimuli, are dysfunctional in autism. These include the search of LTM, and the comparison of input with memory, both processes associated with the initiation of a response. Niwa et al.'s results must obviously be treated cautiously because of the small sample size. Their use of a Student t-test on such a small sample is questionable.

Courchesne, Kilman, Galambos and Lincoln (1984) found that the P300 wave was evoked in their group of autistics with an IQ > 70. This result implied that nonretarded autistics processed information cognitively. For both groups, *differences in P300 components were observed* across tasks. Sensitivity to differences between tasks is an important index of information processing. It indicates an ability to discriminate. Task sensitivity w 'nd in autistics by Niwa et al. (1983).

Courchesne et al. (1984) found nonretarded a stics differed from age matched normal controls however, in terms of the size of the P300 wave itself. In the autistics the wave was typically only about a quarter of the amplitude to the control group's. This is consistent with the Lelord et al. (1979) and Niwa et al. (1983) reports of reduced P300 amplitude in autism. Courchesne et al. also found that the N800 wave was decreased in amplitude in the autistics. This is consistent with the findings by Lelord et al. (1979) and Martineau et al. (1980) of abnormal activity in that time region. Courchesne et al. suggested that the similarity they found of the autistic evoked response compared to that of normal control children of a younger age, implied a maturational delay.

The Courchesne et al. (1984) findings were replicated by Courchesne, Lincoln, Kilman and Galambos (1985b), who in addition found a difference in sensory modalities, in line

with the difference for modality found by the same group in their brainstem evoked potential study on autism (Courchesne et al., 1985a).

The studies of the Courchesne group (Courchesne et al, 1984, 1985a, 1985b) are of particular interest because of the emphasis they place on attention. The position that the Courchesne group have adopted is that autistics are neither hypersensitive nor hyposensitive to stimulation, but instead that the amount of processing that an input receives is limited, as demonstrated by the attenuated P300 amplitudes. They postulated that information processing was limited in this manner, either because processing capacity was restricted in the autistic, or because the depth of processing was shallow. Either interpretation is consistent with a dysfunction of attention.

In a more recent study on the ERP in autism, Pritchard, Raz and August (1987) examined the P300 and the visual augmenting or reducing of an earlier N100 wave. Reducing is associated with attempting to shut out increasing levels of stimulation, whereas visual augmenting is associated with enhancing receptivity as stimulus intensity increases. They found that autistics did not have significantly different N100 amplitudes compared to normals, but that they were significantly more often N100 augmenters. Pritchard et al. (1987) therefore argued that autistics appeared to be experiencing an overload of stimulus information, implying

that they were hypersensitive.

Pritchard et al. (1987) found no difference in the P300 of the autistics for a no task condition and a target detection condition, whereas normal subjects differentiated between tasks. Pritchard et al. proposed that, in response to visual stimulation, attention resources in autistics were engaged uniformly, and indiscriminately, regardless of task context.

The P300 findings of Pritchard et al. (1987) are not entirely consistent with the Courchesne et al. (1984, 1985b) results. Courchesne et al. (1984, 1985b) reported that autistics were task responsive. Although Courchesne et al. (1985b) found a change in P300 for all tasks for all groups, it was of note that in their autistic subjects this change was only half the magnitude of the response recorded from the normals.

Pritchard et al. (1987) argued that their failure to replicate the Courchesne et al. (1984, 1985b) findings may be related to the difference in sense modality used. Pritchard et al. used visual stimuli, but Courchesne et al. (1984) and Courchesne et al. (1985b) used auditory stimuli. Early studies reported that auditory processing was more impaired than visual processing in autism (Hermelin and O'Connor, 1970). BAEP Peak I may be reduced in autism (Tanguay et al., 1982). Differences in response have been found for different sense modalities in autism (Fein et al., 1981; Courchesne, et

al., 1985a). Thus differences in modality may account for the differences between P300 studies (Courchesne et al., 1984, 1985b; Pritchard et al., 1987) in autism, although a recent report of a developmental bias for vision in normal children, suggests that differences on measures of attention should be expected between different sense modalities (Guttentag, 1985).

Nystagmus Studies in Autism. This area of research has been dominated by the work of Ornitz (1974, 1979, 1983, 1987; Ornitz, Atwell, Kaplan, and Westlake, 1985). Ornitz's position is that the modulation of sensory input and motor output is dysfunctional in autism, and that this centres on a pathology in brainstem, particularly the vestibular system. He has studied nystagmus responses in normal and autistic children. A nystagmus is an involuntary eye movement, which is caused by a lesion in either the vestibular system, or in the surrounding reticular formation. It can be evoked under experimental conditions in normal subjects by rapid rotation, and provides information about the integrity of brainstem structures.

For the purposes of this review, we will discuss only the study done by Ornitz et al. (1985). Since Ornitz states:

> Earlier vestibular studies in autistic children, although demonstrating abnormal responses, have suffered from diagnostic imprecision, failure to control for the effects of visual fixation, or the

> use of idiosyncratic response measures which are difficult to interpret in terms of current models of the vestibulo-ocular response (VOR). (Ornitz et al., 1985, p. 1018)

This means the extent to which valid generalizations may be made from earlier nystagmus studies is limited. I therefore take it that the study by Ornitz et al. (1985) was methodologically sound, and free from the limitations of earlier studies. The Ornitz et al study is an excellent piece of research, and great care has been taken to ensure its methodological rigour.

Ornitz et al. (1985) demonstrated that the primary nystagmus response (eye movement in the direction opposite to rotation) had a prolonged time constant in the autistics. There were fewer nystagmus beats during the secondary nystagmus response (eye movement in the same direction as rotation) in the autistics. This was a puzzling finding since a primary nystagmus is always followed in normal persons by a secondary nystagmus response. It was not clear if this difference was a consequence of the exacting criteria for a VOR adopted in the study, or if some real difference existed in the autistic population.

Given the strict controls used in this study, it was concluded that the observed difference between autistics and normals, on the primary nystagmus response to constant rotation, was not due to developmental delays, retardation,

visual input, sex differences, or level of arousal. These findings are consistent with a dysfunction in the brain stem of the autistics.

As far as attention is concerned, Ornitz et al. (1985) stated that their results do not support the idea that autistics are overhabituated, i.e. under-responsive. Rather, since habituation of the VOR is associated with a shortening of the time constant, the finding that the time constant in autistics was longer, suggested that they were not habituating at all only very slowly. This may mean that the autistics are hypersensitive.

Ornitz (1983) adopted the position that the evidence for brainstem dysfunction in autism implicates a sensorimotor modulation deficit, rather than a dysfunction of arousal, although he did speculate that brainstem arousal systems are involved in the pathophysiology of autism. He placed an emphasis on the modulatory influence of motor systems on attention, and argued that stereotypies provide the autistic with an important source of sensory input.

I close this section, noting that the correlates of central nervous system activity in autism are strongly suggestive of brain dysfunction. Event related potential studies indicate that the processing of sensory information is deviant in autism. This abnormality is present at many stages of information processing, as demonstrated by the brainstem dysfunction studies, and P300 data. In sum, these

visual input, sex differences, or level of arousal. These findings are consistent with a dysfunction in the brain stem of the autistics.

As far as attention is concerned, Ornitz et al. (1985) stated that their results do not support the idea that autistics are overhabituated, i.e. under-responsive. Rather, since habituation of the VOR is associated with a shortening of the time constant, the finding that the time constant in autistics was longer, suggested that they were not habituating at all, or only very slowly. This may mean that the autistics are *hypersensitive*.

Ornitz (1983) adopted the position that the evidence for brainstem dysfunction in autism implicates a sensorimotor modulation deficit, rather than a dysfunction of arousal, although he did speculate that brainstem arousal systems are involved in the pathophysiology of autism. He placed an emphasis on the modulatory influence of motor systems on attention, and argued that stereotypies provide the autistic with an important source of sensory input.

I close this section, noting that the correlates of central nervous system activity in autism are strongly suggestive of brain dysfunction. Event related potential studies indicate that the processing of sensory information is deviant in autism. This abnormality is present at many stages of information processing, as demonstrated by the brainstem dysfunction studies, and P300 data. In sum, these

findings suggest that evoked responses in autism are either (1) delayed or (2) of diminished magnitude relative to the normal population.

Various hypotheses have been advanced regarding the attentional status of autistics on the basis of these studies. Some views suggest a dysfunction of arousal is *primary*, and range from positions suggesting that autism is characterized either by chronic hyperarousal (Hutt et al., 1964) or *hypoarousal* (Rimland, 1964). Others suggest that the locus of the problem lies more directly with attention, and the receptivity to *stimulation*: autistics are seen as excessively open to stimulation (e.g. Pritchard et al., 1987). A more subtle approach suggests that the problem lies in the regulation of components of attention (Courchesne et al, 1984, 1985a, 1985b; Ornitz 1979, 1983). On these views attention is dysfunctional in autism in terms of sensorimotor integration and modulation (Ornitz, 1979, 1983), and the modulation of the sensitivity of attention to stimuli (Courchesne et al., 1984, 1985a, 1985b).

The extent to which CNS electrophysiological variables provide information about attention is somewhat limited. Autonomic measures allow for an analysis of some components of attention, that are not easily apparent in the EEG or ERP. It is to these that we now turn.

Autonomic Nervous System Correlates of Attention in Autism

In this section I consider two physiological systems, the cardiovascular system, and the skin. There are three variables of major interest; (1) pressure related changes in the vascular system, (2) the pattern of cardiac output, and (3) conductivity changes in the skin potential. For completeness I also briefly discuss some other miscellaneous measures, such as respiratory period, and soundfilm microanalysis.

Vascular System Findings in Autism. I first deal with the vascular responses of autistics to stimulation. Sokolov (1958, 1963) postulated that during the orienting response there is a shift in blood flow associated with perception of the stimulus. He suggested that peripheral vasoconstriction occurs in tandem with vasodialation of the blood vessels that serve the skull. He hypothesized that a defence response evoked by high intensity stimuli, is accompanied by vasoconstriction at the forehead and peripheral vasodialation.

However, although this conceptualization is straightforward, it has not been extensively confirmed by experimental data. While digital vasoconstriction has been reported to stimuli of a variety of intensities, the

predicted vascular changes at the skull have been sporadic, and in general Sokolov's predictions of vascular changes have not been confirmed (Siddle et al., 1983). The vascular findings in autistics reviewed below should therefore be interpreted with this in mind.

Cohen and Johnson (1977) took vascular measures of ten autistics over a variety of tasks, which were designed to either facilitate the intake of stimuli, or to increase their rejection. On the basis of Sokolov's (1963) predictions, it follows that sensory intake will be associated with an increase in peripheral vascular resistance (PVR), along with a decrease in peripheral blood flow (PBF). Cohen and Johnson found that mean blood pressure (systolic and diastolic) did not drop during the rests between tasks in the autistic subjects, whereas a significant drop in pressure between tasks was observed in the control groups: normal children, normal adults and atypical (but not autistic) children. This indicated that there was no change in mean blood pressure in autistics in response to the experimental tasks. Pritchard et al. (1987) also found task indifference in autistics, but Courchesne et al. (1984) and Courchesne et al. (1985b), did not. As a group autistics were found by Cohen and Johnson (1977) to exhibit increased PBF, and decreased PVR.

Although Cohen and Johnson (1977) attempted assessment across eight different tasks, they were able to engage the attention of the autistics on only two. On the first of

these (viewing television) autistics showed a significant increase in systolic blood pressure, interpreted by Cohen and Johnson to indicate the rejection of stimuli. The normal and atypical groups showed a decrease in systolic blood pressure. There was no difference between any of the groups on the second task, described only as a "perceptual task".

In a later study, Kootz and Cohen (1981) examined 14 autistics at rest, during a social interaction task, and during a response time task. The tasks were repeated over three consecutive days. A significant group X task interaction was found for PEF, which was greater in the autistics. This was consistent with Cohen and Johnson (1977), and the view that autistics reject stimuli. Mean blood pressure and PVR were both elevated in the autistics on the social interaction task. Kootz and Cohen interpreted this to indicate the normal children's responses to the task, and therefore a lack of responsivity in the autistics.

James and Barry (1980) measured cephalic vasodialation and peripheral vasoconstriction in response to novel visual stimulation in 20 autistic children. They found autistics had significantly higher cephalic vasodialation and greater peripheral vasoconstriction. This vascular pattern was opposite to that reported by Cohen and Johnson (1977) and Kootz and Cohen (1981). James and Barry interpreted their results as indicating that the autistics were hyperresponsive to novel stimulation.

In a larger study, James and Barry (1984) examined the peripheral pulse amplitude response (PPAR) in 40 autistic children. They found that the magnitude of the PPAR was greater in the autistics in response to auditory stimulation, and distinguished them from normal and retarded children.

There were some problems associated with the James and Barry (1980, 1984) studies. James and Barry (1980, 1984) defined *a vascular response as the greatest amplitude change* in the pulse between the prestimulus pulse and a pulse 7 - 12 beats poststimulus. This is a far less precise measure than used by Cohen and Johnson (1977) and Kootz and Cohen (1981), and this limits comparison of results. In the Cohen and Johnson, and Kootz and Cohen, studies the formula for PVR* included PBF. The fact that Cohen and Johnson, and Kootz and Cohen, found PVR to be decreased in autism was therefore related to their finding that peripheral blood flow was increased. Pulse amplitude is a poorer measure of blood flow than vascular resistance, and therefore the measure James and Barry (1980, 1984) used was less accurate than Cohen and Johnson, and Kootz and Cohen.

Kootz, Marinelli and Cohen (1982) compared high and low functioning autistic children. They examined 16 autistic children, again at rest, during social interaction and during a reaction time task. Prior to testing, the children were all trained on the reaction time task. Despite extensive

* PVR = [DBP + 1/3 (SBP - DBP)]/(PBF x 10) where:
SBP = systolic blood pressure, DBP = diastolic blood pressure.

teaching only half of the children reached the criteria for proficiency on the task. Those children that did not reach criterion level had the greater intellectual, linguistic and social impairments, and where described as low functioning.

The tests were conducted in three phases, first the children were given an initial training at their school. Then six months later a reminder session was given at their school. Finally, a week after the reminder training, the children were tested in the laboratory. Kootz et al. (1982) found a significant difference in the reaction time of the children across settings. For the high functioning group the reaction time remained relatively constant, whereas performance decreased for the low functioning group, getting worse from initial session to reminder session to laboratory session. Peripheral blood flow of the low functioning autistics was elev ·d over that of the high functioning autistic children for all conditions. This was in line with Cohen and Johnson (1977) and Kootz and Cohen (1981).

In the higher functioning autistics a clear change in the pattern of the PBF response was discernable between tasks. The low functioning group was not responsive to changes in task. This is interesting, since it suggests that the inconsistencies between P300 studies for task responsiveness (Pritchard et al., 1987; Courchesne et al., 1984, 1985b) may be related to differences in the degree of functioning in the autistic children used as subjects in

these experiments.

Cardiac Related Findings in Autism. One of the earliest reported studies on the autonomic nervous system in autistics was by MacCulloch and Williams (1971, cited in Ornitz, 1983, 1987). They found that heart rate variability was greater in autistics than in normals. They argued that the observed variability in cardiac response could reflect the activity of the reticular formation, to what would normally be considered insignificant stimuli.

Cohen and Johnson (1977) found a lack of responsivity was also evident in their heart rate (HR) measures across different tasks: rest, social interaction and reaction time. These findings were replicated by Kootz and Cohen (1981), who noted a failure of heart rate to differentiate between tasks. These studies found that HR was more variable in autistics, and that their mean HR was higher than the controls'. These elevated rates were not related to the unfamiliarity of the testing situation, as later investigation showed the same elevation when HR was recorded at the autistics' schools (Cohen and Johnson, 1977).

On the basis of these findings, Cohen and Johnson (1977) and Kootz and Cohen (1981) suggested that autistics where hyperaroused, and that their failure to respond to stimulation reflects a disruption in the mechanisms of attention. They argued that the autistic cardiac response indicated an attempt to limit sensory input. Following the

work of Lacey (1967; Lacey and Lacey, 1970), they proposed that this was achieved by tonically elevated *HR*, which facilitated the rejection of stimulation.

Given that I examined cardiac and biochemical variables in autism, it is interesting to note that Cohen and Johnson (1977) speculated that the cardiac related attention dysfunction they found might be related to an abnormality in the dopaminergic systems of the brain. Kootz and Cohen (1981) suggested that the noradrenergic system could be implicated in the attentional dysfunction they observed in autism.

Kootz et al. (1982) found that HR did not distinguish between their high functioning and low functioning autistic groups. The low functioning group showed a gradual decline in HR over the three days of testing, and they speculated that this indicated the habituation of this group to the laboratory. Kootz et al. argued that their results indicated that the normal attentional mechanisms of orienting to novelty were dysfunctional in the autistics, and that this had a wide range of consequences, as seen in the symptoms of the syndrome.

Palkovitz and Wiesenfeld (1980) investigated cardiac changes in 10 autistic children under three task conditions: socially meaningful speech, nonsense speech and auditory tones. This study differed from those described above, in that it related changes in cardiac function directly to a

stimulus, rather than to a task condition. The Palkovitz and Wiesenfeld study was the first evoked cardiac response study in autism. In much the same way as EEG data provides information about the tonic aspects of attention, the cardiovascular studies of the Cohen group index generalized responsivity, and not immediate phasic responses to stimulation. Evoked cardiac responses are more illuminating as regards attentional functioning.

In contrast to Cohen and Johnson (1977) and Kootz and Cohen (1980), Palkovitz and Wiesenfeld (1980) found no difference in mean tonic heart rate between autistics and normal age matched controls.

In relation to phasic stimulation, Palkovitz and Wiesenfeld (1980) found a significant difference in the evoked cardiac response between the autistics and the normals for all three different tasks. In the normal controls the cardiac response was decelerator for all conditions. The autistic subjects' responses to auditory tones showed an acceleratory tendency, which did not differ significantly from their prestimulus baseline. In other words, they showed a failure to orient to a socially meaningless stimulus. For the meaningful speech and nonsense speech conditions the autistics showed an initial orienting decelerator response to the stimuli, which was followed by a significant acceleratory trend. The autistics failed to habituate to any of the tasks, whereas clear habituation profiles are

obtained for the normal controls.

Palkovitz and Wiesenfeld (1980) interpreted their findings to denote a major abnormality in the mechanisms which control attention in autistics. The generally *accelerator*y trend to stimulation suggested that they were rejecting stimuli, and were hyporesponsive. Following Graham and Clifton (1966), Palkovitz and Wiesenfeld argued that the input of information into attention may be characterized as defensive in autistics. Palkovitz and Wiesenfeld did not speculate on the significance of the failure of the autistic subjects to habituate. A habituation failure implies a dysfunction in basic associative cognitive processes. This will be taken up later.

The second ECR study to be done in autism was by James and Barry (1984) on 40 autistic children. They found that the magnitude of the ECR was larger in autistic children, than in mentally retarded or normal children. Autistics showed the greatest deceleration in response to stimulation. This finding was opposite to that of Palkovitz and Wiesenfeld (1980).

James and Barry (1984) measured heart rate from the peripheral pulse. A recent study showed that because of pulse transit time, the peripheral pulse is a far less accurate measure of cardiac activity than the ECG (Barry and Mitchell, 1987). This makes the validity of the cardiac measures used in the James and Barry study questionable.

Respiratory Period Studies in Autism. Only two studies have examined respiratory period in autistics. James and Barry (1980, 1984) found that respiratory pause, defined as the percentage increase in respiratory period for the cycle containing the (novel) stimulus, over the prestimulus cycle, differentiated the autistics from normal and retarded subjects. The most marked result of these studies was the finding that respiratory period did not habituate to repeated presentations of the stimulus in the autistic subjects, whereas a clear habituation profile was established for the normals and retardates. This failure to habituate respiratory period was consistent with Palkovitz and Wiesenfelds' (1980) result of nonhabituation of heart rate, and suggested a dysfunction of attention. There was no significant difference in the mean resting rate of the respiratory period between the autistics and the controls. Interpreting these data, and their vascular data (discussed above) James and Barry (1980) suggested that their findings indicated:

> a degree of hypersensitivity to stimuli. Such a hypersensitivity, combined with abnormalities in habituating mechanisms, could suggest that autistic children are constantly bombarded by a multitude of environmental stimuli. It is conceivable that the stress of such constant sensory stimulation would lead to selective-attentional deficits, abnormal

> perceptual responses, and, ultimately behavioural withdrawal as a defense mechanism. (James and Barry, 1980, p. 545)

Electrodermal Response Findings in Autism. As part of their study of evoked cardiac responses in autism, Palkovitz and Wiesenfeld (1980) included the electrodermal response (*EDR*) *as a dependent variable*. They found a highly significant difference between autistics and age matched normals on their mean resting skin conductance levels. The autistics showed higher *levels, indicating greater arousal*, which Palkovitz and Wiesenfeld interpreted as consistent with their suggestion that attention is 'defensive' in autistics. The relative amplitudes of the EDRs did not *differentiate* the two groups on any of the three experimental tasks. A large difference between the two groups was found for spontaneous EDRs. The autistics had five times as many spontaneous skin conductance responses as the normals.

Like Palkovitz and Wiesenfeld (1980), Stevens and Gruzelier (1984) also found that they could not differentiate between autistics and their controls on measures of electrodermal responsivity and habituation. In this study controls consisted of a normal and a retarded group, each with subjects matched for mental age, and chronological age with the autistics. They cautiously suggested that their data implied that response latency was delayed in autism,

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since autistics showed a greater orienting response to the second member of the stimulus train, rather than the first. This is consistent with those EEG reports of generalized slowing in autism (De Meyer et al., 1973; Ornitz, 1979), and the evoked response potential studies which found transmission differences in autistic subjects (Fein et al., 1981; Tanguay et al., 1982; Gillberg et al., 1983).

In the Stevens and Gruzelier (1984) study, response amplitude showed a decrease over trials only for normal controls, suggesting that the autistics and mentally retarded controls had a slower habituation rate. Stevens and Gruzelier concluded that this may imply that the processes of habituation and sensitization are dysfunctional components of attention in autism.

James and Barry (1984) studied EDR, and found significant differences between autistic, mentally retarded and normal children. Autistics showed the highest levels of skin conductance. Habituation effects were less marked in the autistic children.

The differences between groups on EDR measures found by Stevens and Gruzelier (1984) and James and Barry (1984) were not consistent with the EDR data of Palkovitz and Wiesenfeld (1980), who found no difference between autistics and normals in terms of responsivity.

van Engeland (1984) compared 35 autistics to normal children, child psychiatric patients and mentally retarded

controls. In contradistinction to Palkovitz and Wiesenfeld (1980) he found no difference between the groups on frequency of spontaneous EDRs. However, he did find that there were proportionally more electrodermal nonresponders in the autistic group than in any of the control groups. Although Stevens and Gruzelier (1984) and James and Barry (1984) suggested that habituation rates may be slower in autistics, van Engeland (1984) found no difference between groups on measures of habituation.

van Engeland (1984) split all his experimental groups into two subgroups; a group with a high number of spontaneous skin conductance responses (H), and a group with a low number of skin conductance responses (L).

Amongst the L subgroups, only the autistic subgroup showed any difference by greater nonresponding on the first trial of the stimulus series. This was similar to Stevens and Gruzelier's (1984) report that orienting was delayed in autistics.

Amongst the H subgroups, amplitude distinguished autistics from retardates, but not from normals. Latency differed between autistics and normals, and recovery rate was greater in autistics than in child psychiatric patient controls, or retarded controls.

Since electrodermal orienting response variables are known to covary with IQ (White, 1974 cited in van Engeland, 1984), the data for a subgroup of high functioning autistics

with IQ > 80 were reassessed. The H group showed faster recovery rates than either the normal controls, or the child psychiatric patient controls. van Engeland (1984) proposed that this meant that rather than supposing that autistics are "closed" to stimulation, the faster recovery rates suggest more frequent responses and excessive "openess" to stimulation.

Of the autistic children with an IQ in the normal range, 16% were nonresponders, whereas only about 5% of the normals are electrodermally nonresponsive. van Engeland (1984) suggested that although this difference was statistically significant, these results are not definitive of autism. Nonresponding is not a stable trait, but is state dependent. The findings may therefore be attributable to the demand characteristics of the experiment, rather than any real difference characteristic of autism.

Soundfilm Microanalysis. I conclude this section with a brief review of Condon (1985). Condon has done some interesting work on the entrainment of the body to speech, and other sensory inputs. To examine this relationship he filmed a person speaking or being spoken to. Analysis of the film on a frame-by-frame basis revealed that behaviour is made up of discrete, yet synchronized, "movement bundles", which Condon calls "process units to emphasize their organizational nature" (p. 127). He then fed the soundtrack of the film into an oscilloscope, and filmed the screen of

the oscilloscope. By aligning the oscilloscope recordings of the language with frames of the film of the subject, he was able to detect a synchrony between process units and features in the oscilloscope record, i.e. there was an entrainment between speech and behaviour.

When Condon examined autistic children in this manner, he found multiple entrainment and multiple orienting responses to stimuli, which were not found in normal age and sex matched children. For all onsets of auditory stimuli, autistics showed more stimuli entrained process units than normal children. Normal children have a process unit pattern that decreases in response to stimulation. Instead of a reduction in process units to stimulation, the autistics responded with an increase in the number of process units, by anything from 1 to 23 process units.

Condon found that autistics were self-asynchronous, i.e. whereas normally a person's own process units are in synchrony with their own speech, this was not the case in autistic children (nor dyslexic, nor Parkinson's patients).

When autistics were compared to normals for eye movement orienting responses to sound, they showed twice the number of orienting responses. Condon suggested that the "multiple orienting response may be enslaved in some way to the multiple entrainment" (1985, p. 148). This may mean that the elevated number of process units in autism, are related (perhaps causally) to the increase in perceptual sensitivity

indexed by the relatively increased number of orienting responses.

Condon's (1985) results are supportive of the view that autistics are hypersensitive to stimulation. The relationship of increased orienting to multiple entrainment suggested that there may be a motor component to the attentional deficit in autism.

Summary

The studies reviewed above imply that attention is dysfunctional in autism. However, no clear pattern emerges from the literature, and different studies have often found contradictory results. Two differing interpretations emerge from the literature. On one view, attention is characterized as augmenting stimulation in autism, and on the other attention is seen as biased for reducing sensory input in autism.

The elevated levels of basal heart rate, and the vascular pattern of increased PBF and decreased PVR, were interpreted by Cohen and Johnson (1977), Kootz and Cohen (1981) and Kootz et al. (1982) to indicate a defensive attentional style in autistics, who were described as under responsive and hyperaroused.

Phasic cardiac changes which index attention where interpreted by Palkovitz and Wiesenfeld (1980) to indicate

hyporesponsiveness, and increases in basal skin conductance level were seen as indexing hyperarousal.

An alternative position has been espoused which suggests that autistics are hypersensitive to stimulation. James and Barry's (1980, 1984) vascular responses indicated sensory intake, as did their measures of respiratory period. Delayed EDR [illegible] lack of habituation were seen to indicate a dysfunction of sensitization mechanisms in attention by Stevens and Gruzelier (1984). van Engeland (1984) took faster EDR recovery rates as demonstrating hyperresponsiveness in autism, and this is in line with Condon's (1985) findings of multiple orienting responses in autistic [illegible].

The electrophysiological correlates of CNS activity, cortical and brainstem ERPs, and the nystagmus studies, indicate brain dysfunction in autism. The relevance of these data for attention in autism is linked to the information the psychophysiological correlates of autonomic nervous system activity supply, about the intake or rejection of stimuli. The CNS data is consistent with imbalances in either the 'intake' or the 'rejection' system, and this may mean that it is oversimplistic to conceive of the problem in attention in autism as relating directly to either the intake or the rejection of stimuli. It is more probable that the problem relates to the balance between the two mechanisms, as suggested by Courchesne et al. (1984, 1985a, 1985b).

CHAPTER FOUR -- BRAIN REGIONS IMPLICATED IN AUTISM

The literature, reviewed in the previous chapter, on the electrophysiological correlates of CNS activity in autism, implies that there is a pathology of some kind in the autistic's brain. As the previous chapter also indicated, attention appears to be dysfunctional in autism. It is therefore reasonable to suppose that those regions of the brain involved in attention, may show signs of pathology in autism.

In this chapter I first discuss those areas of the brain implicated in attention. This section is rather brief. The literature on the relation between brain and attention is too massive to review thoroughly here. This section therefore focuses on the brain in attention within the context of the model of attention originally developed by Pribram (McGuiness and Pribram, 1980; Tucker and Williamson, 1984; Pribram, 1980, 1981; Pribram and McGuiness, 1975).

This model of attention allocates a major role to the catecholamines. In this project, catecholamines were assayed in the children. Evidence reviewed in the next chapter suggests that there may be a catecholaminergic involvement in autism. Therefore those areas of the brain that contain catecholamines, may be involved in the hypothesized brain dysfunction in autism, and they are reviewed.

Next, studies which have examined the brains of autistics

are examined. These studies provide the most direct data on pathology of the brain in autism. Finally, some theoretical models of brain dysfunction in autism are briefly reviewed.

Brain Regions Involved in Attention.

The term "attention" covers a wide range of information processing activities, from basic sensory perception, to higher order cognitive manipulations of information that extrapolate meaning. It comes as no surprize therefore, that the areas of the brain implicated in attention span all levels of organization in the brain, from the brain stem, to the cortex (Khomskaia, 1972/1982).

Certain areas of the brain are consistently implicated in attention. These include the reticular activating system, the hypothalamus, the amygdala, the hippocampus, the limbic system and the frontal cortex (Khomskaia, 1972/1982; Pribram and McGuiness, 1975).

The arousal response, or the orienting response, is centered on the amygdala. The amygdala is innervated by efferents from the hypothalamus, which in turn receives afferents from the ascending reticular activating system. The amygdala appears to control orienting and habituation to stimuli by means of two reciprocally acting circuits that connect it to the frontal cortex (McGuiness and Pribram, 1975; Pribram and McGuiness, 1980).

An orbitofrontal pathway appears to be involved in inhibiting responses, and section of this frontoamygdala pathway results in a failure of habituation. A second dorsolateral pathway that connects the amygdala to the frontal cortex is related to the initiation of the orienting response, and damage to these pathways eliminates orienting behaviour (McGuiness and Pribram, 1975; Pribram and McGuiness, 1980). The role of these frontoamygdala fibres appears to be related to the tuning of the organism's response to environmental stimuli, via their connections to the hypothalamus and the reticular formation. This allows for the level of arousal to appropriately controlled (McGuiness and Pribram, 1975; Pribram and McGuiness, 1980).

The areas of the brain involved in activation, or motor readiness, are located within the basal ganglia. The appearance of the contingent negative variation, indicating the operation of expectancy controls in activation, is associated with activity in the basal ganglia and dorsal thalamus (McGuiness and Pribram, 1975; Pribram and McGuiness, 1980). Lesions in the basal ganglia produce characteristic behavioural problems associated with the initiation and execution of movement (Marsden, 1984).

In the Pribram and McGuiness (1975) model of attention, effort is considered to be modulated by hippocampal functioning. The hippocampus is involved with the storage of information in short term memory (Rawlins, 1985).

Anatomical Distribution of the Catecholamines

The models of attention due to McGuiness and Pribram (1980) and Tucker and Williamson (1984) link arousal to noradrenergic functioning and activation to dopaminergic functioning. The account of the distribution of the catecholamines that follows complements the description of the anatomical structures involved in attention given above. Since attention is a complex process, it makes better sense to conceive of its neural basis as depending on the operation of a system of fibres, structures and chemicals, rather than attempting to isolate discrete areas involved in attention.

Noradrenaline. There are two major NA pathways in the brian, the locus ceruleus system and the lateral tegmental system (Moore, 1980). The locus ceruleus system is the most clearly delineated of the two. In the spinal cord descending efferents of the locus ceruleus NA system are found in the gray matter of the dorsal and ventral horns, as well as in the lateral horn, which contains preganglionic cells of the autonomic nervous system (Barr and Kiernan, 1983). These descending noradrenergic spinal pathways begin in the medulla of the brainstem, and are particularly dense in the region surrounding the root of the vagus nerve, which serves the myocardium (Kruk and Pycock, 1978).

The locus ceruleus, which is located in the floor of the

fourth ventricle, is the source of most of the NA in the brain, and has the highest density of NA (Carpenter, 1978; Redmond and Huang, 1979). Three major ascending pathways begin in the the locus ceruleus including the dorsal tegmental bundle, the largest NA projection (Barr and Kiernan, 1983). This bundle passes ventrally into the tegmentum, where it synapses with the median forebrain bundle at the level of the hypothalamus. As the locus ceruleus NA system traverses rostrally and ventrally, it gives off branches which innervate the amygdala, mamillary bodies, hypothalamus, cingulate gyrus and other areas of the limbic system (Moore, 1980). Dorsal NA pathways enter the cortex at the frontal pole, and then course posteriorly to the sensory and association cotexes (Kruk and Pycock, 1979; Tucker and Williamson, 1984).

The lateral tegmental NA system, or ventral NA bundle, as it is occasionally called, begins ventrally and caudally to the locus ceruleus, in the area of the lateral group of the reticular nuclei (Moore, 1980). Ventral NA fibres descend to innervate spinal gray, and ascend to nuclei in the brainstem, hypothalamus and limbic system, as well as areas of the basal forebrain (Kruk and Pycock, 1979; Moore, 1980).

Dopamine. There are four major identified dopaminergic pathways: the nigrostriatal system, the tuber infundibular system, the mesolimbic and the mesocortical systems (Bunney and Aghajanian, 1979).

The tuberoinfundibular system appears to be involved in neurohormonal activity that centres on the hypothalamus and pituitary (Carpenter, 1978; Kruk and Pycock, 1979). This dopamine system is not considered part of the "extrapyramidal" system, or part of the basal ganglia (Graybiel, 1984).

The major DA pathway in the brain is the nigroneostriatal system (Moore, 1980). Cell bodies of this system are located in the substantia nigra, pars compacta and the ventral tegmental area (VMT) (Carpenter, 1978; Moore, 1980), and project to the putamen and caudate nucleus, and to parts of the ventral striatum, including the globus pallidus. The nigrostriatal system also has important connections with the thalamus and the premotor cortex (Barr and Kiernan, 1983; Graybiel, 1984).

The mesolimbic and mesocortical dopaminergic pathways have cell bodies in the substantia nigra, as well as in the ventral tegmental nucleus. The substantia nigra and ventral tegmental area are the source of most of the DA in the brain, since mesolimbic, mesocortical and nigrostriatal DA fibres all have their origin in these areas. The mesolimbic and mesocortical systems are occasionally grouped as a single system by some authors (e.g. Tucker and Williamson, 1984), but this is incorrect (Glowinski, Tassin and Thierry, 1984; Iversen, 1984).

The mesolimbic system is comprised of fibres from the

hippocampus, amygdala and septum, which project to areas in the ventral striatum, particularly the nucleus accumbens, olfactory tubercle and anterior olfactory nucleus (Iversen, 1984; Moore, 1980). The mesocortical DA system is characterised by projections from the prefrontal cortex to the dorsal striatum, including the caudate nucleus and the putamen (Iversen, 1984). Interestingly, dopaminergic innervation of the frontal cortex is confined to the prefrontal cortex (Glowinski et al., 1984).

The mesocortical and mesolimbic DA systems may also be differentiated on the basis of their differential responsitivity to neuroleptic drugs. Mesocortical DA does not show tolerance, whereas tolerance is observed in both mesolimbic and nigrostriatal DA. The turnover of DA is much higher in the prefrontal cortex than in the mesolimbic system (Glowinski et al., 1984).

Brain Areas Implicated in Autism

Damage is sometimes apparent in the autistic brain. DeLong (1978) examined the pneumoencephalograms of autistics and found that the temporal horn of the left lateral ventricle was dialated. The medial wall of the lateral ventricle, which is formed by the medial contours of the hippocampus, was flattened and bulged into the ventricle, and showed atrophy. DeLong hypothesized that a unilateral lesion

of the hippocampus may explain verbal learning difficulties in autism.

Nuclear magnetic resonance imaging was used to compare midsagittal scans of the fourth ventricle in autistic and normal subjects by Gaffney, Kuperman, Tsai, Minchin and Hassanein (1987). Like DeLong (1978), they too found ventricular enlargement. This implied a change in the structures which define the fourth ventricle: the pons, cerebellum and medulla. This result may be of particular significance for noradrenergic functioning in autism, since the locus ceruleus is located at the rostral end of the sulcus limitans on the floor of the fourth ventricle.

Few postmortem examinations of the brains of autistic persons have been performed. In the first published report (Williams, Hauser, Dominick, Purpura, DeLong and Swisher, 1980) autopsied brains of four mentally retarded persons with autistic traits. Their descriptions of the patients suggest that only case 1 was classically autistic. For this case atrophy of the orbitofrontal and and anterior temporal cortex was apparent. No other abnormalities were present in the brain of patient 1. Patient 3 showed similar cortical atrophy to patient 1, as well as reduced density of cerebellar Purkinje cells. Patients 2 and 4 were free from any signs of pathology.

Brain preparations of a 29 year old autistic male, killed in a motor accident were compared with that of a 25

year old normal male who died of a heart attack (Baumann and Kemper, 1985). Cell packing was denser in all layers of the subiculum of the hippocampus. The entorhinal cortex, which is the anterior part of the parahippocampal gyrus, showed increased cell packing of all layers, except in a band of cells, the lamina dessicans, in which cells were sparse. The clear zone of the lamina dessicans usually dissapears in childhood. Its presence in the brain of the autistic indicated a developmental delay.

In the hypothalamus, cell density was increased by 66%. Neurons were fewer, and nerve cell bodies smaller, in the septum of the autistic. In the amygdala, cell size was reduced and cell packing density increased by 28% - 40%. The cerebellum had a marked loss of Purkinje cells, and the cerebellar peduncles were thinned and elongated. This was similar to the pattern of cerebellar pathology reported by Williams et al., (1980). Bauman and Kemper (1985) found the fourth ventricle was enlarged, in line with Gaffney et al. (1987).

Models of Brain Dysfunction in Autism

Damasio and Maurer (1978) and Maurer (1986) postulated that brain dysfunction in autism centres on the mesolimbic and mesocortical dopaminergic circuitry. Damasio and Maurer (1978) saw the motor stereotypies of the autistic as a sign

of a basal ganglia involvement, possibly including part of the thalamus. They argued that because autism can be distinguished from childhood aphasia, the damage is not related to the primary language areas of the brain, but instead is probably related to a dysfunction in the mesial aspects of the forebrain, the cingulate gyrus and the supplementary motor area. With regard to the attention dysfunctions of the autistic, Damasio and Maurer (1978) speculated that an inappropriate control of a parietal command function that normally operates to evaluate the social significance of a stimulus may be responsible for inattention.

Ornitz (1983) has developed a model of brain function in autism, that describes three levels of processing of sensory information. The first level is mediated by the vestibular nuclei and surrounding regions of the reticular formation. The second level involves the convergence of sensory pathways on the medial thalamus. The connections of the medial thalamus to the caudate nucleus and the substantia nigra is emphasized by Ornitz (1983). A third level of processing depends on the functioning of the reticular nucleus of the thalamus, which acts as a gating mechanism for selective awareness, and has connections with the prefrontal cortex (Ornitz, 1983).

Summary

There is some overlap between the areas of the brain that have been speculated to be involved in the pathogenesis of autism (Damasio and Maurer, 1978; Maurer, 1986; Ornitz, 1983) and those areas implicated experimentally (Baumann and Kemper, 1985; DeLong, 1979; Gaffney et al., 1987).

The finding that the hippocampus and hypothalamus show signs of pathology in autism (Baumann and Kemper, 1985; Gaffney et al., 1987) is of particular interest, because these regions of the brain are involved in the normal processes of attention and arousal (Khomskaia, 1972/1982; Pribram and McGuiness, 1975; McGuiness and Pribram, 1980; Tucker and Williamson, 1984).

Influential models of the neuroanatomy of autism implicate the mesolimbic and mesocortical dopaminergic systems (Damasio and Maurer, 1978; Maurer, 1986). This is consistent with a dysfunction of the activation mechanisms in attention (McGuiness and Pribram, 1980), and may also effect higher order motivation and effort (Tucker and Williamson, 1984).

CHAPTER FIVE -- THE NEUROCHEMISTRY OF AUTISM

The literature reviewed in earlier chapters suggests that the cognitive deficits of autistic children may have measurable psychophysiological components. These CNS and autonomic electrophysiological measures of autistics show deviance from normal patterns of responsivity. This suggests that there may brain pathology in autism, and direct postmortem study (Baumann and Kemper 1985) and indirect evidence such as the longer brainstem transmission latencies (Fein et al., 1981; Gillberg et al., 1983; Tanguay et al., 1982) support this view.

What is the nature of this brain pathology? It seems apparent from the literature that *there is no clear lesion in* autism. Anomalies in the physiological correlates of attention imply a pathology of some kind in the underlying neural mechanisms. The data reviewed above is consistent with the view that the problem with the autistic brain includes a neurochemical component. In this chapter the neurochemistry of autism is explored.

Research into the neurochemistry of autism has been motivated by a number of factors, not all of which are related to attention. Much of the emphasis has been on symptom reduction by pharmacological intervention, especially with neuroleptics (e.g. Campbell et al., 1982, 1987). The efficacy of drug treatment is highly variable, and results are

uncertain for individual cases, although in general neuroleptic treatment has proved to be of value in au' sm (Campbell, 1978).

Within a broader pharmacologic context, research on schizophrenia has given rise to a *chemical model of psychotic* syndromes, which postulates a dysfunction in dopaminergic neurotransmitter systems (Crow et al., 1978; Julien, 1981). Given that autism is classified under childhood psychosis (American Psychiatric Association, 1980), and that both autistics and schizophrenics are responsive to neuroleptic treatment, it is reasonable to suppose that the neurochemical pathology of autism may be related to that of schizophrenia. Note, however, that autism and schizophrenia are strictly separated by most authorities (e.g. Rutter and Schopler, 1987). Nevertheless, these similarities do suggest that dopaminergic metabolism may be impaired in autism, whatever its relationship to schizophrenia may be.

A second avenue of research that has been pursued in the study of the biochemistry of autism has been more directly related to an interest in the status of attention in autistics. This work, initiated by the Cohen group (Cohen, Caparulo, Shaywitz and Bowers, 1977; Cohen, Shaywitz, Johnson and Bowers, 1974; Cohen, Young and Roth, 1977; Young, Cohen, Caparulo, Brown and Maas, 1979; Young, Kavanagh, Anderson, Shaywitz and Cohen, 1982), has developed in tandem with psychophysiological studies of autism (Cohen and Johnson,

1977; Kootz and Cohen, 1981; Kootz et al., 1982).

Altogether, the neurochemical findings in autism cover a wide range, and it is necessary to restrict the scope of this review to those neurochemicals that seem to be involved in attention. Current data implicates the catecholamines, dopamine (DA) and noradrenaline (NA), as critically involved in attention (Aston-Jones, 1985; Foote, Bloom and Aston-Jones, 1983; Iversen and Iversen, 1975; McGuiness and Pribram, 1980; Panksepp, 1986; Sara, 1985; Tucker and Williamson, 1984). The review that follows concentrates on dopamine and noradrenaline related findings in autism.

For completeness, I mention that serotonin (5-hydroxytryptophan, 5-HT), also a monoamine, like DA and NA, shows signs of dysfunctional metabolism in autism, and some evidence suggests that the same holds true for the opiod peptides. Autistic symptoms such as motor activity disturbances and distractability show improvement following pharmacologic intervention in the serotoninergic system (August, Raz, Papanicolaou, Baird, Hirsch and Hru, 1984). Although platelet levels of 5-HT have consistently been reported to be elevated in autism (Anderson and Hoshino, 1987; Israngkun, Newman, Patel, Duruibe and Abou-Issa, 1986) it appears that platelet 5-HT is not a measure of neuronal function (Young et al., 1982). The suggestion that elevated platelet 5-HT may be related to mental retardation, rather than autism (Young et al., 1982), has not been confirmed by a

recent study which showed that neither IQ nor items on the Autism Behaviour Checklist, were related to platelet rich plasma concentrations of 5-HT in autistics (Kuperman, Beeghly, Burns and Tsai, 1987).

Other evidence suggests that opiod peptides may be dysfunctional in autism. This group of neurohormones may be involved in neurotransmission (Hokfelt, Elde, Johansson, Ljungdahl, Schultzberg, Fuxe, et al., 1979), although their status as neurotransmitters has not been entirely confirmed (Bachelard, 1981). If peptides do not meet the criteria for neurotransmitters, they are nevertheless indisputably a type of neuromodulator (Hokfelt et al., 1979).

Gillberg, Trygstad and Foss (1982) found that urinary measures of peptide excretion in autistics showed a characteristic pattern in 54% of autistics and 17% of children with other psychoses. This pattern was seen in no other control group. Israngkun et al. (1986) found a peptide chromatogram profile which was characteristic of autism, and identified methionine enkephalin as elevated in autistics. Gillberg, Terenius and Lönnerholm (1985) found no difference in cerebrospinal fluid measures of opiod peptides between autistic and normal children. Sahley and Panksepp (1987) base their sophisticated analysis of the social deficits in autism on a presumed deficit in brain opiod concentrations.

Before I review the catecholamine findings in autism, I give a brief overview of the metabolism of the catecholamines

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Before I review the catecholamine findings in autism, I give a brief overview of the metabolism of the catecholamines

in the brain. This will make what follows much clearer.

Neurotransmitter Metabolism

The catecholamines are those neurotransmitters that contain a catechol nucleus and an amine group. In the brain these products are dopamine (DA), noradrenaline (NA) and epinephrine. Catecholamines occur in the brain, in chromaffin cells of the adrenal medulla, and in sympathetic ganglia. NA and epinephrine are metabolites of DA. The metabolic pathway is as follows (see Figure 1). (In this section the following references were used; Bachelard, 1981; Cooper, Bloom and Roth, 1978; Foote et al., 1983; Julien, 1981; Kruk and Pycock, 1979; Moore and Kelly, 1979; Richards, 1983; Young et al., 1982. All general neurochemical information may be found in these sources, or in any neurochemistry text. Points that are specific to certain authors are referenced accordingly.)

Catecholamine Synthesis. Catecholamine synthesis is catalysed by tyrosine hydroxylase, an enzyme, which hydroxylates the amino acid tyrosine, to produce dihydroxyphenylalanine (DOPA). This initial step is the rate limiting point in the synthesis of catecholamines, and is inhibited by the end products of the metabolic cycle, viz. catecholamines or catechols. During periods of high sympathetic activity a pool of strategic NA is depleted, removing its inhibitory influence on tyrosine hydroxylase.

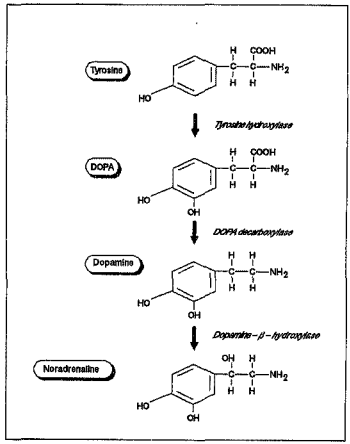

Figure 1. The Synthesis of the Catecholamines.
DOPA = Dihydroxyphenylalanine.

The resultant increase in tyrosine hydroxylase activity reestablishes normal levels of NE, and the negative feedback

loop becomes operational again (Cooper et al., 1978).

There are other mechanisms which operate to control the metabolism of catecholamines over both the short and long term. Short term changes in catecholamine activity tend to increase turnover rate by reducing the affinity of tyrosine hydroxylase for endproduct inhibitors, and increasing its affinity for tyrosine and the relevant metabolic cofactor. Long term alterations in catecholamine synthesis result in an increase in the amount of available tyrosine hydroxylase (Cooper et al., 1978).

Catecholamine synthesis is also mediated by endocrine factors. Levels of circulating adrenocorticotrophic hormone (ACTH) are known to increase catecholamine levels (Kizer and Youngblood, 1978).

DOPA is converted into dopamine by the removal of CO_2 from the amine by DOPA decarboxylase, an enzyme which catalyses a wide range of neuroactive substances. It is of relevance to autism to note in passing that DOPA decarboxylase requires pyridoxal phosphate, a vitamin B_6 derivative, as a coenzyme. DA is then transformed into NA by the action of dopamine-β-hydroxylase, which oxidases a side chain of the amine, and utilizes ascorbic acid as a cofactor.

This pathway is the major pathway of catecholamine synthesis. It has been speculated that catecholamines may also be synthesized by alternative routes. Firstly, tyrosine may converted into tyramine by DOPA decarboxylase, and it has

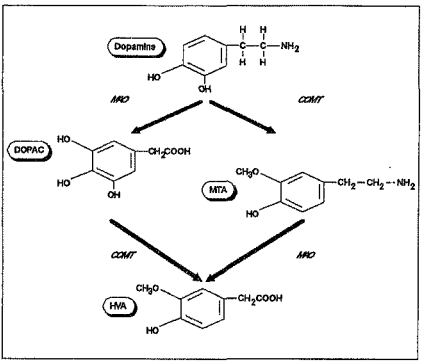

Figure 2. The Metabolism of Dopamine.
MAO = Monoamine oxidase; COMT = Catechol – O – Methyltransferase; DOPAC = 3,4 – Dihydroxyphenylacetic acid; MTA = 3 – Methoxytyramine; HVA = Homovanillic acid.

been observed in vivo that tyramine may be converted into DA in the liver by unknown catechol forming enzymes. Secondly, in vitro studies show that tyramine may be converted into octopamine by dopamine-B-hydroxylase, and then into NA by unknown enzymes (Cooper et al., 1978).

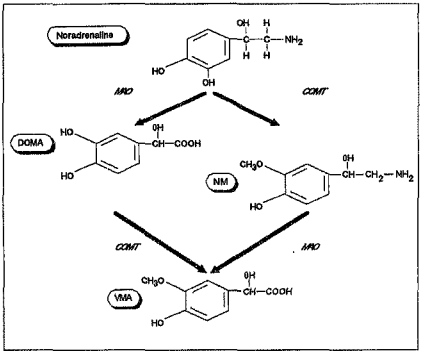

Figure 3. The Metabolism of Noradrenaline to Vanillylmandelic Acid.
MAO = Monoamine oxidase; COMT = Catechol – O – Methyltransferase;
DOMA = 3,4 – Dihydroxymandelic acid; NM = Normetanephrine;
VMA = Vanillylmandelic acid.

Once a neurotransmitter has been synthesized and released into the synaptic cleft, it must be inactivated. This occurs either by the reuptake of the neurotransmitter into the neuron, or by the breakdown of the neurotransmitter into its metabolic byproducts. Since reuptake cannot be measured

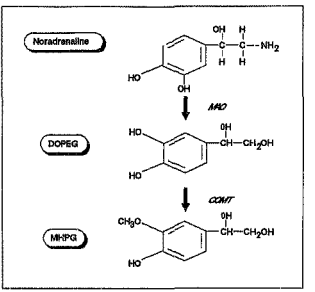

Figure 4. The Metabolism of Noradrenaline to 3 – Methoxy – 4 – hydroxyphenylglycol.
MAO = Monoamine oxidase; COMT = Catechol – O – Methyltransferase;
DOPEG = 3,4 – Dihydroxyphenylglycol;
MHPG = 3 – Methoxy – 4 – hydroxyphenylglycol.

directly (for ethical reasons), it is not discussed further.

Catecholamine Metabolism. Although both DA and NA require monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) for their breakdown, their metabolic pathways are otherwise different. The endproduct of DA metabolism is homovanillic acid (HVA) (see Figure 2). There are two identified pathways for the conversion of DA into HVA. Firstly, DA may be catalysed into 3,4-dihydroxyphenylacetic

acid (DOPAC) by monoamine oxidase (MAO). MAO has two subtypes, MAO_A and MAO_B. MAO_A acts selectively on serotonin and NA (Bachelard, 1981). MAO_B acts on a wider range of amines, including DA (Kruk and Pycock, 1979). DA is therefore catalysed into DOPAC by MAO_B. DOPAC is then converted into HVA by the action of COMT. Secondly, DA may be converted into 3-methoxytyramine by COMT, which is in turn transformed into HVA by the action of MAO_B.

Noradrenaline is metabolized by the following three pathways. For the first two pathways, the endproduct is vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid, VMA) (see Figure 3), and for the third pathway the endproduct is 3-methoxy-4-hydroxyphenylglycol (MHPG) (see Figure 4). Firstly, NA may be converted into 3,4-dihydroxymandelic acid (DOMA) by MAO_A, and then into VMA by COMT (see Figure 3). This is the major metabolic pathway to VMA from NA. Secondly, COMT may catalyze NA into normetanephrine (NM), which is then converted into VMA by MAO_A (see Figure 3). Thirdly, NA is converted into MHPG by the action of MAO_A, which creates 3,4-dihydroxyphenylglycol, which is in turn metabolized into MHPG by COMT (see Figure 4).

In order to assess the functioning of DA and/or NA in autistics some technique must be used that allows activity in the metabolic cycle of the catecholamines to be measured. This may be achieved either directly or indirectly. Typically, this has involved an indirect assessment by means

of the administration of a pharmacological agent with a known chemical action. Alternatively, some element of behaviour that is known to depend on a given neurotransmitter may be assessed, and this may provide some insight into the biochemical status of the patient. With the development of sophisticated techniques in biochemistry it has become possible to directly measure the level of one or more of the *neurotransmitters*, or related substances, in certain preparations, such as plasma or urine. It is particularly with the direct assessment of neurochemicals in autistics that this chapter is concerned, since this study was in the same vein.

Noradrenergic Findings in Autism

One of the earliest studies on catecholamines in autism was conducted by Landgrebe and Landgrebe (1976). Using the thin layer chromatography techniques available at the time, they assayed the urine of 74 autistic subjects. No controls were used. They found traces of DOPAC in 88% of autistics, and VMA in 24%. Other chemicals found are not of relevance to attention, and are not discussed here. It is interesting to compare the sensitivity of this method with the one used in the present study. In this study VMA was routinely assessed in all the children. At issue were the relative concentrations of neurochemicals, not in what percentage of

subjects a given chemical was found.

Noradrenaline and Dopamine-ß-hydroxylase. Lake, Ziegler and Murphy (1977) measured the levels of plasma NA and dopamine-ß-hydroxylase (DßH) in 11 autistic patients, and in their parents and siblings. Compared to age matched normal children, the level of plasma NA in autistics was doubled, and the level of DßH was significantly lower. They found that the level of DßH was significantly reduced in the relatives of the autistics, and that the autistics did not differ from their families in terms of DßH concentration. Lake et al. (1977) did not report the relationships for familial NA. They noted that the relationship between DßH and NA did not follow the expected pattern in autism, since if NA levels are elevated, then the levels of its precursor, DßH, should be elevated too. In the Lake et al. study, blood samples were taken after a 20 minute rest period. They speculated that their finding of elevated NA levels may reflect the failure of the autistics to reach normal basal level during the rest period because of chronic hyperarousal. More recently Israngkun et al (1986) found plasma NA to be significantly elevated in 14 autistic subjects, compared to 10 age matched normal controls.

The relevance of increased plasma NA for attention is undermined by the fact that plasma NA is not of central origin (Anderson and Hoshino, 1987). This does not entirely rule out a peripheral involvement of NA in attention. For instance, the cardiac controls on attention require the operation of

peripheral neural mechanisms (Graham, 1962; Lacey, J.I., 1967; Lacey, B.C. and Lacey, J.I., 1970, 1974; Natelson, 1985). Lake et al.'s (1977) results remain applicable to attentional functioning in autism, despite this coda. In fact, the origin of any biochemical must be taken into account when *interpreting its relevance*, particularly for psychological functions that are known to involve a central nervous system component.

Some of the Lake et al. (1977) findings were not confirmed by Belmaker, Hattab and Ebstein (1978), who reported DβH to be elevated in 15 children with functional psychosis. The Belmaker et al. (1978) study is not directly comparable to the Lake et al. study. Whereas Lake et al. compared autistics to normals, Belmaker et al.'s (1978) controls were a group of 10 children diagnosed with brain damage or mental retardation. Furthermore, Belmaker et al. placed autistic and childhood schizophrenic patients into the same category. Differences between the autistic and childhood schizophrenic groups were not reported, as they did not approach statistical significance, supposedly because of the small numbers involved. Belmaker et al. speculated that their finding of elevated DβH may indicate hyperarousal in autism.

In 1986 Garnier, Comoy, Barthelmy, Leddet, Garreau, Muh and Lelord examined plasma DβH in 19 autistic children. Compared to normal children there were no significant DβH differences in the autistic group. However, plasma DβH was

elevated in higher functioning autistics over low functioning autistics. No differences were found between the low functioning autistics and the normal children. Following, Lake et al. (1977) and Belmaker et al. (1978), Garnier et al. (1986) suggested that autistics may be chronically hyperaroused.

Thus, as far as DBH is concerned, the whole range of possible findings have been observed in autism; Lake et al. (1977) found decreased levels, Belmaker et al. (1978) reported increases in DBH, while Garnier et al. (1986) found no difference. These authors have all suggested that their DBH findings imply a noradrenergic involvement, however the direction of any predicted changes may not be as expected, as Lake et al.'s finding of increased plasma NA levels and decreased DBH indicated.

3-Methoxy-4-Hydroxyphenylglycol. Young et al. (1979) studied 24 hour levels of urinary MHPG in five autistic boys, and found MHPG to be significantly decreased compared to age matched normal males. It will recalled that on the basis of their cardiovascular findings, Kootz and Cohen (1981) speculated that there may be a noradrenergic involvement in autism. Young et al. suggested that an alteration in NA activity may explain the impaired regulation of attention, arousal and anxiety in autism, and be related to its involvement both centrally and autonomically, especially in the control of cardiovascular functioning.

findings of Young et al. (1979) were not replicated in a study by Gillberg, Svennerholm and Hamilton-Hellberg (1987), who found levels of cerebrospinal fluid (CSF) MHPG did not differentiate autistic subjects from sex and age matched normal controls. It therefore appears that the drop in MHPG observed by Young et al. may be attributable to their small sample size.

In sum the data implicating a noradrenergic involvement in autism is equivocal. Direct measures of NA activity do not consistently show a difference between autistic and other groups, and most of the support for the noradrenergic hypothesis comes from extrapolation from the data (reviewed above) indicating that arousal and attention may be dysfunctional in autism.

Dopaminergic Findings in Autism

Homovanillic Acid. Evidence for a dopaminergic involvement in autism is much stronger than the comparable NA data. The first published report of relevance examined levels of CSF HVA and 5-hydroxyindoleacetic acid, the major serotonin metabolite, in 9 autistic children, 11 atypical children and 10 epileptic children (Cohen et al., 1974). The experimental procedure involved admitting the children to hospital, and putting them on a course of probenecid prior to the lumbar

puncture. Levels of HVA were significantly different between the three groups. The mean for HVA in autistics was lower than the in atypical group. The mean of the epileptic group is not available from the data Cohen et al. reported. The range of the values for the autistic group was greater than in the atypical group.

The same experimental procedure as Cohen et al. (1974) was adopted by Cohen et al. (1977a) except that they used different control groups; other childhood psychosis, central processing disturbance, childhood aphasia and pediatric patients who were relatively normal. They found that autistics exhibited the greatest range of values, particularly for HVA, but that overall there were no significant differences between the groups, except for 5-hydroxyindoleacetic acid.

Both the Cohen et al. (1974, 1977a) studies used probenecid, a membrane blocker which prevents the active transport of acid metabolites of neurotransmitters from the CSF. Administering probenecid prior to a lumbar puncture was believed to give a more accurate measure of central neuronal function than otherwise. However, there are numerous methodological problems associated with the use of probenecid, which seriously impede the analysis of CSF samples obtained after probenecid administration (Winsberg, Hurwic, Sverd and Klutch, 1978).

In CSF studies by Gillberg et al. (1981) and Gillberg and

Svennerholm (1987), in which probenecid was not used, dopaminergic dysfunction in autism was more clearly implicated than by Cohen et al. (1977a). Levels of HVA were significantly elevated in autistics, and showed a greater range than normal sex and age matched control children. Of all the groups examined, only the autistics showed an isolated increase in HVA. In all the other groups there was either no increase, or the increase was associated with an increase in the levels of MHPG of and/or 5-hydroxyindoleacetic acid. In this sense the autistics differed from other childhood psychoses control groups. These results also suggested that the increase in HVA was not associated with mental retardation. In the mentally retarded groups HVA levels fell within the normal range, and there was no correlation between HVA levels and IQ for any of the groups. In their studies, Gillberg et al. (1983) and Gillberg and Svennerholm (1987), found that HVA was also elevated in controls with progressive encephalopathy, and those with meningitis.

In addition to plasma DBH levels, Garnier et al. (1986) examined levels of urinary HVA, which was found to be elevated in autistics. A negative correlation between HVA and DBH in high functioning autistics was reported, but the pharmacologic reason for this was not clear.

Reports currently in press, or in preparation (Minderaa et al., cited in Anderson and Hoshino, 1987) found no difference between autistic and normal children for either

plasma HVA, urinary HVA, or urinary DA.

Pyridoxal Phosphate. Some interesting results have been obtained with the use of vitamin B_6 in autism (Rimland, Callaway and Dreyfus 1978; Lelord et al., 1982). These results are of relevance to dopaminergic function in autism, although this is sometimes overlooked in reviews (e.g. Young et al., 1982). As noted in the section on catecholamine metabolism, pyridoxal phosphate (vitamin B_6) is a necessary cofactor in the catabolism of DOPA to dopamine.

Rimland et al. (1978) assessed behavioural differences before, during and after treatment with vitamin B_6 in a double blind study, and found a significant increase in autistic symptoms on cessation of treatment. Since vitamin B_6 may also interact with the serotonergic neural system, Rimland et al. interpreted their findings as consistent with elevated levels of plasma serotonin in autism. They noted that the observed differences may have been the result of a dopaminergically based change.

Dopamine has been more directly implicated by the vitamin B_6 studies of Lelord, Callaway, Muh, Arlot, Sauvage, Garreau and Domenech (1978), and Lelord et al. (1982). Lelord et al. (1978) examined urinary levels of HVA before and during vitamin B_6 therapy. They found that compared to a normal controls, the autistics had elevated pretherapy levels of HVA. Treatment reduced the levels of HVA in autistics, and was associated with a reduction in symptoms. Their results were

replicated by Lelord et al. (1982), who in addition found that average evoked potentials showed a "normalization" by treatment. Vitamin B_6 treatment was associated with changes in the evoked recordings in both autistic and normals.

Metabolic Enzymes. Next I discuss reports which examined levels of platelet MAO in autism. Platelet MAO is associated with MAO_B, rather than MAO_A (Cohen, Young and Roth, 1977b), and therefore these findings apply to dopamine, not noradrenaline. Cohen et al. (1977b) studied 31 autistic individuals who were found not to differ significantly from normal controls. Lake et al. (1977) found that autistics did not differ from their relatives, nor from normal controls for levels of platelet MAO. Neither did clinical populations differ from each other; MAO levels were similar in autistic, childhood schizophrenic, mentally retarded and brain damaged patients (Belmaker et al., 1978).

Belmaker et al. (1978) also found that COMT, the other major catecholamine enzyme, was not significantly different in autism. Since COMT is involved in the degradation of both NA and DA, this finding is relevant to both systems, subject to the limitations of the Belmaker et al. study discussed above.

Blink Rate. Lastly I briefly review some studies which implicate a DA involvement in autism, but did not measure DA or related compounds directly. Blink rate, an index of dopaminergic activity (Schelkunov, Kenunen, Pushkov, and Charitonov, 1986; Stevens, 1978), was measured in 15 autistic

children, and was found to be significantly higher than in normal controls (Goldberg, Maltz, Bow, Karson and Leleszi, 1987). This sharply distinguished the autistics from a mentally retarded group which had lower blink rates than normal. These results indicated that elevated DA turnover was not related to mental retardation, but to the psychiatric syndrome of autism.

Pharmacotherapy. Haloperidol, a DA antagonist, significantly facilitates learning and decreases maladaptive behaviour in autistics (Campbell et al., 1982). Given the vital role of DA in motor function, it might be expected that reducing DA turnover would decrease the frequency of stereotypies in autism. Strangely, stereotypies were not decreased by haloperidol treatment (Campbell et al., 1982).

In a recent review of the pharmacological treatment of autism, Campbell et al. (1987) concluded that autistic symptomology is best treated by DA agonists, such as haloperidol, than other pharmacologic compounds.

Summary

Catecholamine metabolism seems to be disturbed in autism. The evidence for a noradrenergic involvement in autism is equivocal. Although plasma NA has been shown to be elevated by Lake et al. (1977), other measures of noradrenergic activity, such as concentrations of MHPG (Young et al., 1979;

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Summary

Catecholamine metabolism seems to be disturbed in autism. The evidence for a noradrenergic involvement in autism is equivocal. Although plasma NA has been shown to be elevated by Lake et al. (1977), other measures of noradrenergic activity, such as concentrations of MHPG (Young et al., 1979;

Gillberg et al., 1983; Gillberg and Svennerholm, 1987) do not favour a noradrenergic involvement in autism.

The most consistent catecholamine finding in autism has been an elevated level of HVA, the endproduct of dopamine metabolism. Levels of CSF HVA were shown to be elevated in autism by Gillberg et al. (1983) and Gillberg and Svennerholm (1987). Similar findings were reported for urinary HVA by Lelord et al. (1978, 1982), and Garnier et al (1986). Disconfirmatory results were obtained by . (1974, 1977a) for CSF HVA, but there were method. roblems with that study. Negative results were also reported to have been found by Minderaa et al. (in press, cited in Anderson and Hoshino, 1987) for urinary and plasma HVA.

The higher concentrations of HVA in autism probably indicated an increase in the turnover rate of DA in the nervous system, and increase in the rate at which it is biosynthesized. Since MAO and COMT levels are normal in autism (Cohen et al., 1977; Lake et al., 1977; Belmaker et al., 1978), the source of the elevated HVA levels must lie in the synthesis of DA, rather than in its breakdown. This view is supported by interventions in DA synthesis which have therapeutic benefit (Campbell et al., 1982, 1987). The study of Landgrebe and Landgrebe (1976) found a higher percentage of biochemicals related to catecholamine synthesis, than biochemicals related to their breakdown, in the urine of autistics.

There is good reason to conclude that there is a biochemical involvement in autism. In particular it appears that dopaminergic metabolism is characterised by increased turnover.

The literature discussed to this point suggests that attention is dysfunctional in autism, and that dopaminergic metabolism is disturbed. Is there any relation between the neurochemical imbalances in autism, and the attention deficits that have been observed? Any attempt to answer this question must consider the relationship between attention and neurochemistry.

CHAPTER SIX -- ATTE TION AND NEUROCHEMI STRY

What role do the catecholamines play in the modulation of attention? It should not be thought that catecholamines are the only neurochemicals that have been implicated in the control of attention. Acetylcholine, for instance, is believed to be involved in attention and memory (Panksepp, 1986). However, in this project the focus is on the catecholamines.

The neurochemical basis of attention may be studied in two kinds of subjects. Firstly, the neurochemical status of patient populations with known attention deficits may examined. Secondly, the effects of pharmacological manipulations on attention may be explored in experimental animals. Both kinds of study are reviewed in this chapter. In order to provide a perspective on these data, I first briefly discuss theoretical views on the relationship between attention and neurochemistry.

Theoretical Positions on Attention and Neurochemistry

The most comprehensive theoretical treatments of the neurochemical basis of attention are McGuiness and Pribram (1980) and Tucker and Williamson (1984). Tucker and Williamson (1984) drew strongly on McGuiness and Pribram (1980), who in turn based much of their argument on the model

of attention delineated by Pribram (Pribram, 1980, 1981; Pribram and McGuiness, 1975). Recall that this model, discussed above, identified three control mechanisms on attention: arousal, activation and effort.

McGuiness and Pribram (1980) described the activation system as based on dopaminergic controls, which were modulated by acetylecholine, and the arousal system as dependent on the operation of noradrenal ne, which was modulated by serotonin. The effort mechanism identified by McGuiness and Pribram (1980) fell under the control of opiod peptides. The strength of the McGuiness and Pribram model lies in its neuroanatomical and neurophysiological basis. Some of this information has already been discussed in earlier chapters. The McGuiness and Pribram neurochemical postulates are largely speculative, and based on evidence which only indirectly implicated NA and DA in attention.

Tucker and Williamson (1984) extended the model of attention developed by McGuiness and Pribram (1980). They discarded the effort construct, since they argued that components of effort may be better explained by reference to higher order properties of the activation system, which allowed for voluntary (effortful) motor acts. Thus opiod peptides have no role in the Tucker and Williamson model. The Tucker and Williamson model attempts to illuminate the nature of the arousal and activation processes by reference to the properties of noradrenergic and dopaminergic

neurotransmission, respectively.

The theoretical import of the Tucker and Williamson (1984) model lies in their recognition that the pattern in which certain neurochemicals function, may make them best suited to modulating particular psychological functions that operate in a similar manner. For instance, one of the properties of noradrenergic neural transmission includes firing in response to sensory evoked orienting behaviours (Aston-Jones, 1985; Foote et al. (1983); Sara, 1985). The excitability of the *locus ceruleus is modulated by a system* of inhibitory NA fibres, which inhibits locus ceruleus firing in *response to external environmental* stimuli, which might otherwise inappropriately disrupt ongoing behaviour. This operational property may make the NA neurons best suited for modulating the control of organism by external inputs. The point of the Tucker and Williamson model is an attempt to link the effects of DA or NA on neurons in the brain, to the behavioural effects of these same neurochemicals.

Animal Studies on the Neurochemistry of Attention

Noradrenaline and Attention. NA is involved with modulating the level of arousal, and covaries *with sleep-wake* cycles (Balechard, 1981). Arousal is a major component of attention (*Davies, 1983; McGuiness and Pribram, 1980*). This suggests that arousal as a component of attention may be

modulated by NA. Furthermore, noradrenaline turnover changes in response to the presence of environmental stimuli (Foote et al., 1983), irrespective of whether a response is elicited from the organism or not (Iversen and Iversen, 1975). This is consistent with the role assigned to NA by Tucker and Williamson (1984) in the 'What is it?' orienting response.

NA has been implicated in learning, since various tasks that require the establishment of learned contingencies are affected by NA manipulations (Iversen and Iversen, 1975; Panksepp 1986). Oke in (1978) suggested that ability of NA pathways to regenerate and reorganize was consistent with their alleged role in associative thinking and learning. The role NA plays in learning may be accomplished by the capacity of noradrenergic fibres to inhibit neuronal discharge in the sensory cortices, while amplifying the signal-to-noise ratio of incoming stimuli (Aston-Jones, 1985; Foote et al., 1983; Sara, 1985). This mechanism may provide the basis of NA's hypothesized role in selective attention (Panksepp, 1986). A neural mechanism of this kind is compatible with the role ascribed to NA in orienting by Aston-Jones (1985), McGuiness and Pribram (1980) and Tucker and Williamson (1984).

On the basis of studies on the stump tail monkey (Macaca arctoides) in which either the locus ceruleus was stimulated, or NA antagonists or agonists were administered, Redmond and Huang (1979) concluded that the NA was involved in the modulation of fear and anxiety. NA was consistently

implicated in the operation of the fight-flight mechanism. Redmond and Huang postulated that this mechanism operated at different levels of intensity. At moderate levels they suggested that it functioned as a cautionary device, and at low levels as "a novelty detector, a stimulus enhancer or an *attention focuser*" (*Redmond and Huang*, 1979, p. 2159). Only at high levels of NA activation was a fight-flight response elicited. Their data supports the hypothetical role of NA in orienting responses.

Tucker and Williamson (1984) have postulated that noradrenaline controls the habituation bias in attention. The operation of the habituation bias primes the organism for novelty. For Tucker and *Williamson the neuronal model, and* the match-mismatch process involved in orienting is based in noradrenergic control.

Tucker and Williamson (1984) suggested that the role of NA in orienting was partially a result of the modulation of reward by NA. While it is now accepted that reward in the intracranial selfstimulation paradigm is modulated by DA (Stein, 1978), Tucker and *Williamson have argued that NA is* important to motivated interactions with the environment. The well documented involvement of noradrenergic mechanisms in the control of satiety, drinking and feeding (Iversen and Iversen, 1975) may be related to this type of motivated environmental interaction.

Motor Control and Dopamine. The role of DA in the control of motor behaviour is well documented. Parkinson's disease is the result of decreased levels of DA in the basal ganglia, particularly in the nigrostriatal pathway, and is usually treated by administration of L-DOPA, a precursor of DA (Iversen and Iversen, 1975; Marsden, 1984). Corpus striatum pathology is also associated with tremors, athetosis, choreas and ballism (Carpenter, 1976).

Animal studies of the role of DA in movement are particularly interesting. Extrapyramidal Parkinsonlike symptomology may be induced in animals by treatment with 6-hydroxydopamine (6-OHDA), a dopaminergic neurotoxin, or by administration of chlorpromazine, a DA antagonist (Iversen and Iversen, 1975). Administration of apomorphine or d-amphetamine, both DA agonists, results in motor stereotypies, in which an element of the normal behavioural repertoire is endlessly repeated (Dickinson and Curzon, 1983; Iversen and Iversen, 1975). The parallels between these repetitive behaviours and autistic stereotypies are very suggestive.

In vivo analysis of neurochemicals in freely moving, conscious rats has been accomplished with the application of newly developed voltammetry push-pull perfusion techniques (Freed, 1986). Dopamine metabolism showed an increased turnover rate in rats trained to circle for a water reward. DOPAC levels were increased in the substantia nigra on the

side contralateral to the turn, and decreased on the ipsilateral side. This asymmetry was normalized after circling movements ceased. There was a 300% increase in DOPAC levels after 20 minutes of turning. Freed's (1986) results are in effect a replication of the classic studies by Ungerstedt (1971, cited in Iversen and Iversen, 1975), except that Ungerstedt induced DA asymmetry by treatment with 6-OHDA, and Freed trained his rats to turn.

On the basis of studies which implicated DA in movement, and in the induction of stereotypies, Iversen and Iversen (1975) suggested that dopaminergic mechanisms may function like a motor probability generator. On this view the effects of apomorphine administration are explained as the increasing the probability of a narrow range of behaviours. As the level of DA increases, so behaviours become increasingly species specific and more stereotyped.

Iversen and Iversen postulated that DA was involved in controlling response arousal mechanisms. The failure of an animal to respond after lesions to dopaminergic systems, may indicate a disruption of arousal, rather than be directly related to movement inhibition in a straightforward manner.

This position was given a more sophisticated treatment by the model of movement proposed by Evarts and Wise (1984) which emphasized the importance of higher order control in the sequencing of behaviours. The successful execution of planned movements requires behavioural units to be executed in the

appropriate sequences. An important function of DA appears to be the higher order control of motor sequences. This skill appears to be dysfunctional in Parkinson's patients (Marsden, 1984), and manifests as a disruption of the motor plan in teleological behaviours.

Stereotypies in autism may be the result of a breakdown in the control of voluntary movements caused by elevated DA, turnover. Animal studies show that excessive DA stimulation causes stereotypies (Dickinson and Curzon, 1983). The nature of the deficit in Parkinson's disease, particularly the disruption of higher order control over movement suggests the failure of similar mechanisms in autism. Disruption of normal DA metabolism appears to impede the correct selection of a motor plan unit from amongst the possible alternatives (Everts and Wise, 1984; Marsden, 1984). This failure to make the appropriate selection may parallel the consequences of dopaminergic metabolic imbalances on the control of sensory attention.

Sensory Control and Dopamine. The discussion has emphasized the motor components of dopaminergic systems up to this point. Ungerstedt (1971, cited in Iversen and Iversen, 1975) proposed that the function of DA in behaviour had to do with the activation of the striatum by arousing sensory stimuli. Ungerstedt suggested that the normal role of DA was concerned with sensitization and the initiation of appropriate responses. For Ungerstedt the lack of responsiveness observed

after destruction of DA pathways by 6-OHDA was indicative of a sensory loss.

There is evidence that DA is involved in cognitive processes. Low doses of haloperidol facilitate active avoidance, but similar doses of amphetamine cause a delay in the extinction of active avoidance, and facilitate passive avoidance (Kovacs and De Wied, 1976. cited in Oades, 1982). It appears that when DA transmission is increased it becomes more difficult for the animal to make the link between changed stimulus conditions and appropriate changes in avoidance behaviour. This indicates a selection dysfunction.

The role of DA in cognition is also evidenced by the finding of an increase in striatal DA synthesis during the performance and acquisition of a fixed ratio operant task (Heffner and Seiden, 1980). In this study DA turnover in the caudate nucleus and putamen was positively correlated with the number of lever presses made by the experimental animals. No changes in DA turnover were found in the hypothalamus of in the mesolimbic area.

Rats trained on a delayed alternation task on a T-maze showed deficits in both the accuracy and latency of their responses after destruction of DA A10 cells by 6-OHDA (Simon, Scatton and Le Moal, 1980). The A10 cell group is situated in the rostral portion of the brain stem, and includes the ventral tegmental area (VMT). There are projections from the VMT to the prefrontal and striatal cortex as part of the

mesocortical and mesolimbic dopaminergic systems. The destruction of DA cells in the brain stem impaired the retention of a learnt response. Simon et al. (1980) commented that:

> The experimental animals showed postoperatively more collateral or 'irrelevant' behaviours because they presented attentional deficits manifested by an enhanced distractability or responsiveness to environmental stimuli. This renders the animal unable to select relevant information. (Simon et al., 1980, p. 151).

Simon et al. (1980) speculated that the prolonged latency of the response in 6-OHDA treated animals was indicative of a motivation deficit. Stein (1978) postulated that catecholamines were necessary for reward behaviours, and were involved in motivation and affect. Furthermore, it is dopamine that is specifically involved with reward behaviour: destruction of NA fibres by 6-OHDA caused no change in the selfstimulatory behaviour of rats, but destruction of the DA pathways caused *significant changes in the pattern of* selfstimulation in experimental animals (Stein, 1978). Stein argued that DA provided the arousal necessary for selfstimulation. He noted that administration of haloperidol, a DA antagonist, blocked selfstimulatory behaviour.

The role of DA in exploratory behaviour was examined by Fink and Smith (1980). They selectively destroyed DA neurons in rats using 6-OHDA injected into the anterior lateral

hypothalamus, and then tested each animal by placing a novel wooden cube in an alcove in the animal's home cage. The number of approaches made into the alcove were used as an index of exploratory behaviour. Lesioned animals showed a reduction in the number of approaches. This was not a due to a failure to notice the cube, because the latency for the first response was the same in both experimental and control animals. Nor was it due to a deficit in general activity level in treated animals, since photocell counts of activity were the same in all animals.

The number of approaches in treated animals could be increased by administration of apomorphine, a DA agonist. Of interest was the finding that apomorphine reduced the number of exploratory behaviours in untreated rats. Fink and Smith (1980) also found that the effect of apomorphine could be reversed in the 6-OHDA animals the treatment with pimozide, a DA receptor antagonist.

All substances administered to the experimental animals were radioactive. In subsequent analysis of the animals' brains, Fink and Smith (1980) found a lack of fluorescence in the nucleus accumbens, olfactory tubercule, deep layers of the frontal cortex and the anterior cingulate gyrus. There was a loss of cell bodies from the ventral tegmental area (A10). No fluorescence was observed in the caudate nucleus of these rats, as might have been expected. Their results indicated that DA afferents from the VMT were

necessary for the exploration of novel environments.

These results were important because they indicated that exploratory behaviour was reduced by both the destruction of DA fibres, and the pharmacological induction of acute dopamine supersensitivity. Thus dysfunction is observed when DA metabolism is both increased and decreased. The response curve takes the familiar inverted "U" shape. This is consistent with Iversen and Iversen's (1975) assertion that normal striatal responsiveness depends on the level of DA mediated arousal.

The function of DA in exploration may be understood as controlling the orienting response to novel stimuli. In the case of the Fink and Smith (1980) the untreated rats oriented to the novel stimuli. The act of going into the alcove to examine the stimuli, is well accounted for by Ohman's (1979) theory of the orienting response: the initial novelty of the stimulus elicits a call for processing capacity. This was followed by a voluntary exploration of the alcove.

These studies implicate DA in cognitive processes and suggest a role for DA in the processing of sensory stimuli. Direct evidence for a role of DA in sensory information processing was produced by Chiodo, Antelman, Caggiula and Lineberry (1980), who found that single unit recordings of the substantia nigra's zona compacta showed discharges in response to sensory stimulation. Chiodo et al. suggested these responses were not involved in the transmission of specific

sensory information, because they occurred for different modalities, but were instead related to the role of DA in the behaviourally activating properties of sensory stimulation.

Chiodo et al.'s (1980) interpretation of their results was confirmed by Camp and Rudy (1987) who showed that behavioural activation in rat pups was inhibited by haloperidol and facilitated by administration of L-DOPA or apomorphine. It is interesting to note that behavioural activation as defined by Camp and Rudy referred to highly stereotyped behaviours such as suckling, and this is consistent with Iversen and Iversen's (1975) contention that elevated DA increases stereotyped species specific behaviours.

Blocking is a conditioned learning phenomenon in which animals are conditioned by reinforcement to respond to a stimulus (CS_A). The same stimulus is then paired with a second stimulus (CS_B) to form a compound stimulus (CS_{AB}), and responses are again reinforced. Under these circumstances the CS_B provides no new information about the reinforcing event. When the stimuli are subsequently presented separately to the animals, and without reinforcement, the animals should show greater responding to the CS_A and a blocking of response to the CS_B, since they had previously learnt that the second stimulus carried no additional information about reinforcement. Blocking thus represents the operation of a selective attention mechanism.

Using a blocking paradigm, Crider, Solomon and McMahon

(1982) treated rats with amphetamine. They found that blocking was abolished in the treated animals, but was unchanged in untreated rats. These results indicated that an increase of DA turnover resulted in a selective attention deficit. Crider et al. (1982) were able to abolish the blocking deficit by administration of haloperidol.

A recent report by Crider, Blockel and Solomon (1986) showed that prolonged treatment with haloperidol, which induces DA supersensitivity, also resulted in a selective attention deficit in rats, a evidenced by the failure of rats treated with DA antagonists to block responses to CS_B.

Concerned that the failure to block responses in the haloperidol treated rats was the result of a hyperresponsiveness, rather than a selective attention deficit, Crider et al. (1986) conducted a second experiment. In this study they introduced a novel click. They found that responses to the click were equivalent for the treated and untreated animals. This indicated that the treated animals were not responding to just any stimulus, and showed no signs of hyperresponsivity. Instead these results indicated that the haloperidol treated rats were unable to ignore the CS_B, even though the information it carried was redundant. *Crider et al. (1986) suggested that their results indicated an* attentional perseveration, much like the perseverative stereotypies induced by the administration of amphetamine or apomorphine. Animals first attended to, and then failed to

tune out stimuli that carried no information value.

Beninger (1983) noted that nonresponses in animal studies of the DA system are frequently the result of sensory neglect, rather than a motor deficit. Rats with 6-OHDA lesions of the substantia nigra showed a neglect for stimuli *on the side* contralateral to the lesion. The opposite effect was observed in rats treated with unilateral intrastriatal injections of DA. These animals showed enhanced responsivity to *stimuli contralateral to the injection*. *Beninger* concluded that the problem faced by these animals was interfacing sensory inputs with response systems.

This line of thinking was extended *by Lidsky, Manetto and* Schneider (1985) who argued persuasively that one of the major functions of the basal ganglia in the control of movement was their ability to gate sensory inputs into the motor system. They saw the DA rich basal ganglia functioning as sensory analyzers for motor systems.

These findings of dopamine involvement in sensory aspects of attention run contrary to the model of dopaminergic control developed by Tucker and Williamson (1984). On their model DA is allocated a minimal role in sensory processing, its major function is motor control, although Tucker and Williamson do ascribe some importance to DA in the integration of perceptual and motor information. The studies discussed above imply a far greater role in sensory processing and selective attention to DA than the Tucker and Williamson model does.

Attention Dysfunctions in Other Clinical Populations

Dopaminergic dysfunction is characteristic of a number of neuropsychological syndromes associated with attention dysfunction. This data provides further evidence for the role of DA in attention.

Attention Deficit Disorder. The Diagnostic and Statistical Manual (III) of the American Psychiatric Association (1980) defined two forms of attention deficit disorder (ADD), one with associated hyperactivity (ADDH) and one without (ADD). Reviews of the neurochemistry of ADD (Raskin, Shaywitz, Shaywitz, Anderson and Cohen, 1984) and of hyperactivity (Shaywitz, Shaywitz, Cohen and Young, 1983) indicated that urinary HVA was unchanged, levels of CSF HVA measured using probenecid loading were decreased, MHPG was lowered, and platelet MAO_B appeared to be reduced, in hyperactive ADD children. Both Raskin et al. (1984) and Shaywitz et al. (1983) concluded that ADD and ADDH may be associated with a dopaminergic abnormality. This position is complemented by the clinically well documented effect of methylphenidate (a DA agonist) in ameliorating ADD symptoms.

In autistics methylphenidate decreases skin conductance response, as it does in ADD children, indicating lowering of arousal levels (Mokrid et al., 1987). The relevance of neurochemical findings in ADD to autism was also indicated by

the similarity in peptide profiles found between ADD children and children with early onset childhood autism (Mokrid et al., 1987). Interestingly, this characteristic profile was distinct from the profile obtained from children diagnosed with delayed onset childhood autism (and who therefore did not meet the DSM III criteria for autism).

Although there does appear to be some evidence that autism and ADD have a common neurochemical profile characterized by disturbances in DA metabolism, the evidence for a DA abnormality in ADD is far less compelling than that for autism. Nevertheless, these data do support the position that DA is implicated in attention dysfunction.

Schizophrenia. Schizophrenia is associated with abnormalities in attention (Oades, 1982), and as I have noted, it has been hypothesized to be caused by a dopaminergic imbalance (Crow et al., 1978; Julien, 1981). The dopamine theory of schizophrenia traditionally stated that DA turnover was increased in schizophrenics (Crow et al., 1978), but recent data suggests that DA may be reduced in institutionalized schizophrenic patients (Karoum, Karson, Bigelow, Lawson and Wyatt, 1987). Nevertheless, the direction of the concentration gradient may not be as important as the finding of a DA metabolic disturbance in schizophrenia.

The administration of DA agonists, such as amphetamine, are known to produce acute psychotic states akin to schizophrenia (Crow et al., 1978; Iversen and Iversen, 1975).

Neuroleptics, which interact with dopaminergic chemistry, usually by blocking DA reuptake, are useful in the pharmacological treatment of schizophrenia. These data suggest that there may be some relationship between dopaminergic dysfunction and attention in schizophrenia.

Korsakoff's Psychosis. Korsakoff's syndrome is usually the result of alcoholic poisoning, but may also be caused by trauma to the brain, and is associated with specific cognitive and sensory deficits. These patients show anterograde amnesia, which appears to be due to their increased sensitivity to proactive interference, in which little new information can be retained because of interference in short term memory processes caused by established memories (Butters, 1978). Korsakoff's syndrome is often accompanied by lesions of the hippocampus, although it now appears that the most consistently observed lesion in the syndrome is in the dorsal medial nucleus of the thalamus (Butters, 1978). Lesions of the hippocampus caused abnormal indistractability in monkeys (Pribram and McGuiness, 1975), which may indicate a habituation failure in these animals. Lesions of thalamic nuclei are also associated with attention deficits, particularly those which fit into the neglect syndrome (Heilman, 1978).

Thus, it may be that Korsakoff's patients have a dysfunction in attention, although the nature of the dysfunction is in all probability clearly distinguishable from

that observed in autism. It is interesting to note that MHPG and HVA levels are reduced in Korsakoff's psychosis, and that this decrement is directly associated with cognitive deficits, as measured by the Weschler Adult Intelligence Scale and other psychometric batteries, in these patients (Mair, McEntee and Zatorre, 1985).

Mental Retardation. One of the methodological issues in research on autism is whether or not any observed symptoms are the product of autism, or if they are related instead to retardation associated with autism (Yule, 1978). The literature reviewed in earlier chapters indicated that autistics may be differentiated from mental retardates by both electrophysiological and neurochemical measures. It has been found that CSF levels of 5-hydroxyindoleacetic acid, HVA and NA were significantly elevated in young Down's syndrome subjects, as compared to normal age matched controls. In older Down's syndrome patients, NA and 5-hydroxyindoleacetic acid are still elevated, but HVA levels are not (Kay, Schapiro, Riker, Haxby, Rapoport and Cutler, 1987). This result indicates that while autism and mental retardation are separate and distinguishable syndromes, they may share some similar monoaminergic mechanisms, and on the basis of the foregoing discussion, it is reasonable to conclude that these may be associated with an attention deficit.

The common thread of dopamine pathology in the neuropsychological syndromes just described suggests that it

is part of the pathogenesis of these syndromes, and manifests as a cognitive-affective attention dysfunction in the patient. Swerdlow and Koob (1987) have proposed a model of dopamine dysfunction that centres on a cortico-striato-pallido-thalamic loop. This forms the basis to their analysis of DA pathology in schizophrenia, mania and depression. They stated:

> The goal of this approach is not to understand the etiology of a single disease, but rather to study how dysfunction in a single brain system contributes to similar behavioural abnormalities in different disease processes. (Swerdlow and Koob, 1987, p. 202)

The behavioural abnormalities to which Swerdlow and Koob (1987) referred are related to attention dysfunctions of the kind discussed above. On their model, the neural basis of these dysfunctions is to be found in the mesolimbic and mesocortical dopaminergic pathways. It is illuminating to quote Swerdlow and Koobs' description of the function of the corticostriatal interface:

> This circuitry functions to allow the NAC [nucleus accumbens] to select and maintain particular sets of impulses originating in limbic structures and frontal cortex. These impulses form the basis of emotional and cognitive processes which are narrowed and amplified by the intrinsic Spiny I matrix of the NAC; ongoing emotional and cognitive processes are reinforced while conflicting impulses are 'filtered'

> or suppressed. Thus, the primary function of dopaminergic activity in this hypothesized circuitry is to modulate the capacity of the intrinsic Spiny I matrix to 'filter out' irrelevant patterns, 'initiate' new patterns, or 'switch' existing patterns of cognitive and emotional information. (Swerdlow and Koob, 1987, p. 203-204)

Summary

The studies reviewed in this chapter indicated that attention has a neurochemical basis. Animal studies of noradrenergic function show that it is involved in orienting to stimuli. The data is consistent with the model of the neurochemistry of attention proposed by McGuiness and Pribram (1980) and Tucker and Williamson (1984).

Animal studies of the role of DA in attention are less supportive of the McGuiness and Pribram (1980) and Tucker and Williamson (1984) models. The role of DA in motor activity is related to higher order processes, such as the sequencing of behaviours and the choice of appropriate acts from the animal's repertoire (Evarts and Wise, 1984; Iversen and Iversen, 1975; Marsden, 1984). Dopamine appears to be critically involved in the sensory components of attention, particularly the selection of stimuli (Crider et al., 1982, 1986; Simon et al., 1980). Selective attention may have a

dopaminergic basis.

Clinical groups with attention deficits show signs of DA pathology. The model of DA functioning in mental illness developed by Swerdlow and Koob (1987), assigns important attention related functions to DA, such as switching between stimuli and filtering stimuli. It is interesting to note the close overlap between the brain areas they implicate, and the areas implicated by Ornitz (1983) and Damasio and Maurer (1978) in the pathophysiology of autism.

CHAPTER SEVEN -- METHOD

Subjects

Autistics. Of 36 autistic children included in the study, 20 were drawn from the Unica School for Autistic Children, Pretoria, and 16 from the Johannesburg Autistic School, Johannesburg. The age of the children ranged from 4 to 14 years. The average age was 8.86 years. There were 24 males and 12 females.

Nine children were on medication at the time of the experimental procedures. Three were taking Tegratol: two had been for 2 years, and one for 18 months. One of these children was suffering from Douchene's muscular dystrophy. A further three were on Meleril. Of these, one had used Meleril for 5 months, and another for an unspecified time. The other child, had been on Meleril for 8 months, and had discontinued use for 4 months prior to testing. Since there was a remote possibility that some residual pharmacologic effect was present, this child was placed in the medication group. The other three children on medication had been taking Zaditern, Neulactal and Epilim for 2 months, 2¼ years and 5¼ years, respectively. All the other autistics had been medication free for at least six months prior to the commencement of the study.

A letter explaining the exp(imental procedure was sent

to the parents of all the children, requesting their permission for the inclusion of their child in the study. Parents who allowed their children to participate signed a written consent form, and completed a protocol specifying their child's biographic details.

Admission to the two autistic schools was usually made on the basis of recommendations by either a team of clinical psychologists and psychiatrists, or by an experienced neurologist. These professionals made their diagnoses using the Diagnostic and Statistical Manual (DSM III) of the American Psychiatric Association (APA, 1980).

However, since this procedure was not applied to all admissions, an additional diagnosis was made by me for each child using the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis and Daly, 1980; Schopler et al., 1985). Of the diagnostic scales currently available, the CARS is the most extensively tested, and appears to be the most reliable scale (Parks, 1983). The diagnosis was made on the basis of observations of the child, and discussions which I had with each child's teacher. Six children who fell into the 'not autistic' category of the CARS were excluded from the study.

Controls. The issue of what constitute appropriate controls for research in autism remains contentious (Kistner and Robbins, 1986). Yule (1979) has argued convincingly that controls should include a group of equivalent mental age to

the autistics. This requirement frequently takes the form of including a group of mentally retarded children as a control group (Kistner and Robbins 1986). Although it was originally planned to include an mentally retarded control group in this study, this proposal was not accepted by the Ethics Committee of the University of the Witwatersrand. Therefore, although not having a mentally retarded control group compromised the methodological rigour of this study, one was not included.

A control group of normal children was used. While some authorities have contended that matching is not necessary, since the relevant variables are unknown in autism (Campbell, 1978), it was decided to match for age and sex. Sex is well known to be skewed in favour of males in autism (Rutter, 1978), and this was apparent from the 2:1 ratio of males to females among the autistic children used in this study. Since cardiac responsivity is known to vary with age (Graham, Anthony and Zeigler, 1983), and since biochemical variables may vary with age, it was decided to match for age.

Normal age and sex matched children were drawn from the Ridge School, Johannesburg and Auckland Park Preparatory School, Johannesburg. Written parental permission was obtained before testing began. None of these children were on any medication, nor had been for six months prior to the experiment.

Cardiac Variables

Cardiotachometer Apparatus. Interbeat interval (IBI) was measured using a cardiotachometer (Buttress, manuscript in preparation), loaned by the National Institute of Personnel *Research. IBI is defined as the latency period between* successive occurrences of the R wave, which appears in the electrocardiogram (ECG) as the peak of the QRS complex, and corresponds to the depolarization and contraction of the ventricles.

Cardiac activity can be measured as either rate or period. The most basic unit of measure of heart period (HP) is interbeat interval (IBI). The most common measure of heart rate (HR) is beats per minute (BPM). There is some question as to whether HR or IBI is the better measure, since transformations from IBI to HR are nonlinear (Siddle and Turpin, 1980). It has been argued that the transformation of raw IBI data into HR introduces errors into the means, variance and degree of skewness of the transformed data, and that these errors have the effect of obscuring small evoked cardiac responses in the ECG (Khachaturian, Kerr, Kruger and Schachter, 1972). Others have suggested that converting the frequency distributions of groups from IBI to HR, skews the resultant HR frequency distribution away from normality, and that this results in introduction of statistically significant differences between groups (Jennings, Stringfellow and Graham,

1974).

Graham (1980) demonstrated that these effects were an artifact of the method of computer simulation used in those studies, and were not related to a statistical transformation error.

The output of the cardiotachometer was a d.c. voltage. A 5 V output signal was equivalent to an IBI of 1000 msec, a 2.5 V signal corresponded to an IBI of 500 msec, and so on. Testing the equipment indicated that the input was directly proportional to the output for voltages below 10 V, but that an exponential nonlinear relationship between input and output appeared when voltages exceeded 10 V. Since 10 V was equivalent to a 2 sec IBI (or 33 beats per minute), and IBI almost never exceeds this value (except in the dying), it was decided not to correct for this nonlinearity.

The cardiotachometer utilized an analog-to-digital/ digital-to-analog (AD-DA) processor. Cardioelectric activity was read from the electrode leads attached to the subject, and then amplified. Each time an R wave was detected a timer was set to zero. When the next R wave occurred, the timer value was stored in memory and the timer reset. The digital value in memory was then transformed by the AD-DA processor into an analog voltage output proportional to the IBI.

Cardiac activity was monitored during a 5 minute foreperiod, to establish the subject's mean IBI. There is no standard length of time over which basal HR or IBI is

established. It has been suggested that adaptation periods of at least 15 minutes should be used (Hastrup, 1986), because this reduces that chance of making a Type II error, since the longer the adaptation foreperiod the lower the mean HR reported. This finding is of course not surprising. If the adaptation period was long enough the subject would fall asleep, resulting in even lower mean HRs. After consultation with the staff of the autistic schools involved in the study it was decided that 5 minutes was about the longest an autistic child could be expected to sit still. Indeed, some children fidgeted so much during the foreperiod that the session had to be terminated and restarted after the child quietened down.

Electrodes. As is customary, Ag/AgCl (silver-silver chloride) electrodes (Beckman, Inc., U.S.A.) were used to detect the R wave. This metal, compared to other electrode metals, is the least prone to drift in the potential baseline, and therefore gives the most accurate and reliable measure of current flow (Stern, Ray and Davis, 1980). The skin was first lightly abraded to remove the stratum corneum. A small amount of electrode adhesive paste (Beckman EEG Adhesive paste, Beckman, Inc., U.S.A.) was placed on the electrode site, and the cup of the electrode filled with paste. The electrode was then secured in place using an electrode collar and standard electrical insulation tape.

The leads where connected to the subject as follows. One

lead was affixed to the right clavicle. The other was attached to the left 6th or 7th rib, and an earth was connected to the left ankle. None of the standard limb lead connections were appropriate when examining autistic children, because limb leads are more susceptible to distortion by movement artifacts, whereas leads to the torso are not as prone to artifacts (Brener, 1980; Stern et al., 1980). Furthermore, the torso lead configuration used was the one recommended for use on the cardiotachometer.

Computer Apparatus. The output of the cardiotachometer was fed into channel 0 of a 16 channel, 12 bit unipolar AD-DA card (FPC-010, Peter's Computer Imports, N.S.A). The card was installed in an 16 bit microcomputer using a 9088 central processing unit running at 8 MHz (Computer Warehouse CW16 Excel, N.S.A.). The output channels of the AD-DA card where read at the input port of the computer using instructions assembled in GWBASIC (Microsoft Corp., U.S.A.). Each subject's IBI data were stored in the random access memory of the computer until the end of the experimental session, at which time they were saved to disk for later analysis.

The rate at which the computer samples the cardiotachometer, and the cardiotachometer the subject, is of relevance for two reasons. Firstly, to avoid losing information, the computer should read the input port from the AD-DA card at least as fast as the smallest possible IBI, minus the computer processing time. If this were not the

case, then depolarization of the myocardium could occur and not be detected, because the computer would be engaged in processing previous signals. Secondly, because this particular cardiotachometer used IBI as the output, error was constant for any given period. This had the necessary consequence that error was nonlinear with respect to rate. Under these circumstances resolution must be of the order of 1 msec if the error is to remain less than 1 beat at typical rates (Graham, 1980). The AD-DA card sampled the cardiotachometer every 60 μsec. The rate at which the cardiotachometer sampled the subject was unknown, but was estimated to be of the same order as the resolution of the AD-DA card in the computer. This was well below the 1 msec limit discussed by Graham (1980).

Stimuli. In order to elicit an orienting response rather than a defence response or a startle response, the physical and temporal properties of the stimuli used in a psychophysiological experiment need to be precisely controlled. It is known that stimulus intensities above the prepain range evoke defence responses. Sokolov (1963) identified this as range as between 65 - 85 dB for auditory stimuli. Subsequent research has modified estimates of the prepain range, which is now considered to lie between 75 dB and 95 dB (Turpin, 1986). It was therefore decided to use 60 dB SPL (sound pressure level) stimuli to ensure that an OR was elicited, and not a defence or startle response. Stimuli were

delivered through Grason-Stadler headphones (Model D1, Grason-Stadler, U.S.A.).

Each stimulus was of 2 sec duration. Stimulus duration does not appear to be a relevant variable, since physiological responses are known to be similar for stimuli of between 2 to 30 sec duration (Graham, 1982).

Although stimulus duration does not effect the kind of physiological response elicited by the stimuli, the rise and fall time of the stimuli do (Turpin, 1986). Stimuli which have no controlled rise and fall times elicit startle responses or transient detecting responses, rather than ORs, even if they fall below the prepain range in intensity (Graham et al., 1983; Graham, 1979, 1982). The stimuli were therefore given rise and fall times of 200 msec each, with a plateau of 1600 msec (see Figure 5).

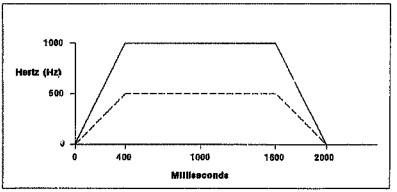

Figure 5. Stimulus shape, showing rise and fall time.
The first 14 stimuli were 1000 Hz each (solid line). The 15th was 500 Hz (dotted line).

In order to test for the presence or absence of orienting, habituation and dishabituation, a train of 15 stimuli were u d. To elicit orienting, stimuli had the physical properties described above, and were novel for all subjects. The interstimulus interval was 2 sec. The first 14 stimuli were all 1000 Hz. Repeated presentation of identical stimuli should result in habituation of the physiological response (Sokolov, 1958, 1963). The last stimulus was 500 Hz. A change in the physical properties of the stimulus should elicit a dishabituation response, in which the subject re-orients to the stimuli (Sokolov, 1958, 1963).

Test Conditions. Each session was conducted in a quiet classroom at the child's school. All the children were familiar with the class in which the testing was conducted. This experimental situation was chosen in preference to the laboratory. It was rationalized that since autistic persons frequently display intolerance to a change of environment, moving them to a laboratory may impose a pattern on the cardiac data that would override any effect that may be due to the experimental manipulation, possibly obscuring relevant data. In normal children a change i: tonic HR has been measured over consecutive days of testing, and attributed to habituation to the laboratory environment (Kootz and Cohen, 1981). A similar pattern is found amongst autistic children (Kootz and Cohen, 1981), and appears to be greater for lower functioning autistics, than high functioning autistics (Kootz,

et al., 1982). Thus the greater the degree of autism, the larger the cardiac response to the novelty of the laboratory.

A familiar environment was therefore used in the testing in an attempt to control for this effect. Of course this meant that environmental variables which are known to influence IBI, such as temperature and humidity, were not controlled. All recordings where done between 8.30am and 1.30pm, over a period of five weeks.

Each session was begun once the child had become accustomed to the electrodes. In seven cases, autistic subjects were unable to accommodate to the electrodes, and testing had to be discontinued. Thus for the cardiac data the size of the autistic sample decreased from 36 to 29.

Once the 5 minute foreperiod was complete, and basal HR had been established, the computer sent a 5 V pulse via the AD-DA card which activated the auditory stimuli. Presentation of the *stimuli lasted one minute*, and the *session* concluded with another minute of recording.

Biochemical Assays

Although CSF and blood provide accurate indices of brain metabolism, the invasiveness of the associated procedures proscribed their use. Therefore the urine of the subjects was assayed. Of the biological fluids that can be obtained noninvasively (urine, sweat, saliva), urine is the fluid of

choice (Christie and Woodman, 1980). Since the urine contains neurotransmitters and metabolites produced by both the CNS and peripheral nervous system, it is a less accurate index of brain than CSF.

Chromatographic techniques have been enhanced by high performance liquid chromatography with electrochemical detection (HPLC-ED) (Davidson and Fitzpatrick, 1985; Kodama and Nakata, 1984). HPLC-ED may be used to measure the concentration of neurochemicals in a variety of preparations, including urine. The technique is sensitive and exact. The Department of Medical Biochemistry, University of the Witwatersrand, which is equipped with HPLC-ED, was approached, and agreed to assist with assays.

A search of the HPLC literature was conducted to find a method which allowed for the simultaneous determination of NA, DA, MHPG, and HVA, and which was compatible with the HPLC equipment at the Department of Medical Biochemistry. Some methods returned values for all the monoamines, their metabolites, and amino acid precursors (e.g. Oka, Kojima, Togari and Nagatsu, 1984), but were complex and difficult to use. A relatively simple technique described by Bockstaele, Dillen, Claeys, and De Potter (1983), was modified, and the final assay returned values for NE, DA, MHPG, VMA and HVA concentrations.

A technician was employed to set up the HPLC equipment, and to begin running assays. Once the experiment was in

progress a member of staff at the Department completed the assays.

Urine Collection. Urine specimens were collected from the first urine of the morning. They were temporarily stored on ice in 50 ml urine specimen bottles containing 1 ml 6M HCl (hydrochloric acid). Once in the laboratory, aliquots of 2.5 ml were prepared and stored at -20° C until required.

For the normal children only one urine sample was taken. For each autistic child it was decided to take three urine samples. This was only achieved in 9 cases; from 19 two samples each were taken, and from 8 only one sample each was obtained. When more than one sample was taken, the assays were averaged to give the final concentration value for that child.

Sample Workup. For each assay two test tubes were each filled with 1 ml aliquots of defrosted urine. To one test tube 1 ml of internal standard was added, and to the other 1 ml of double distilled water. The internal standard consisted of 2 mg/ 100 ml of DA, HVA, MHPG, VMA, and 1 mg/ 100 ml of NA. Thus, for each subject there was one spiked sample and one unspiked sample. The spiked aliquot contained catecholamines in quantities approximately equal to those expected in the sample. The difference between the spiked and the unspiked samples was used to determine the concentration of the catecholamines (Bockstaele et al., 1983).

Half a millilitre of trichloracetic acid (TCA) was added

to each test tube to deproteinize the urine. The tubes were mixed on a vortex and then kept in the refrigerator for 10 minutes to allow for protein precipitation. Next, they were centrifuged at 3000 rpm at 4° C for 10 minutes. The supernatant was removed, and filtered using a 2 ml sterile syringe fitted with Millex HV4 filter unit (Millipore, U.S.A.). Twenty microlitres (20 µml) of filtered supernatant was then injected into the column of the HPLC.

Apparatus. The HPLC analyses were performed using a LKB 2150 HPLC pump (Bioanalytical Systems, U.S.A.) equipped with a Spherisorb C18 reverse phase column 250 mm by 4.5 mm (Phase Separations, Britain). The HPLC was also fitted with a 7 µml protective Brownelle guard column RP18 (Phase Separations, Britain). All the HPLC tubes were stainless steel or teflon. Electrochemical detection was done with a Bioanalytical Systems LC-4A detector (Bioanalytical Systems, U.S.A.) with a carbon paste working electrode and a Ag/AgCl reference electrode.

Mobile Phase. The running buffer consisted of 950 ml double distilled water, to which 0.82 g (0.1 M) CH_3COONa (sodium acetate) and 50 mg disodium EDTA (ethylene diamine tetraacetic acid) was added. The EDTA was used to stabilize the catecholamines, which are known to be unstable at alkaline pH (Davidson and Fitzpatrick, 1985; Taylor, Ried, Geddes and Curle, 1983). A precise pH of 4.0 was obtained by using glacial CH_3COOH (acetic acid). This further stabilized the

catecholamines. Lastly, 50 ml of MeOH (methanol) was added. The final solution therefore contained 5% MeOH.

The flow rate of the HPLC was set to 1.0 ml/ min, with a resultant pressure of 92 bar. The potential for the electrochemical detection was +0.8 V against the reference electrode. The detection range was ~100 nA. All equipment was filtered and degassed daily prior to use.

Quantitative Analysis. Concentration of neurotransmitter or metabolite was based on the comparison of the spiked to the unspiked sample chromatogram, according to the equation:

$$X = \frac{Ax(\text{unspiked})}{Ax(\text{spiked}) - Ax(\text{unspiked})} * Y$$

where;

X = amount of metabolite X in the aliquot, and

Y = amount of added metabolite in the spiked aliquot (Bockstaele et al., 1983).

Peak areas were integrated using a 3390A Integrator (Hewlett-Packard, U.S.A.) to give a final concentration value in mg/d.

Data Analysis

Data analysis was done using Statpak (NorthWest Analytical, Inc., U.S.A.) on a micro computer equipped with an

8088 processor. Input files for Statpak were created by exporting data in ASCII (American Standard Code for Information Interchange) format from spreadsheets made with Framework II (Ashton-Tate, U.S.A.).

The HPLC chromatogram gave concentrations for catecholamines (NA, DA) and related metabolites (MHPG, VMA, HVA) as mg/d. Following the rationale of the data analysis procedure used in the National Institute for Mental Health's Collaborative Program on the Psychobiology of Depression (Secunda, Koslow, Redmond, Garver, Ramsey, Croughman, et al., 1980) it was decided to subject the biochemical data to *further analyses, as used by Maas, Koslow, Davis, Katz, Frazer, Bowden, et al.,* (1987).

This involved calculating the ratios between precursors and products for the following: DA/HVA, DA/NA, NA/MHPG, NA/VMA and MHPG/VMA. Next, an estimate of total catecholamine synthesis (CA) was obtained by summing the concentrations of DA, HVA, NA, MHPG and VMA. This was used to determine the following ratios of specific neurochemicals to the total synthesis of catecholamines: DA/CA, HVA/CA, NA/CA, MHPG/CA, VMA/CA. Precursor-product ratios provide an index of turnover rate, and ratios that have CA as the denominator index an aspect of the relationship between a specific neurochemical and catecholamines in general. This latter measure provides a measure of the interaction between noradrenergic mechanisms and dopaminergic mechanisms.

CHAPTER EIGHT — RESULTS

Cardiac Variables

Since cardiac responsivity to the auditory stimuli was examined, IBI was first converted to heart rate, since events in real time are not comparable to events in cardiac time (Graham, 1978)

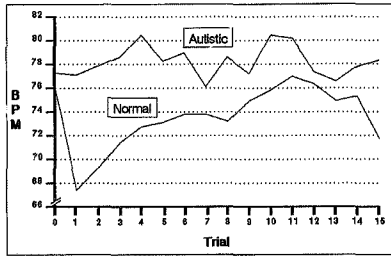

Figure 6. Mean heart rate for each trial.
BPM = beats per minute.

Heart rate was analyzed using a two way analysis of variance for repeated measures (Wilson, 1967). There was a significant difference between the evoked cardiac response of

the autistic children and the normal children (F = 16.27, df = 1/56, $p < 0.01$). Heart rate showed significant changes over time (F = 41.22, df = 15/15, $p < 0.01$). The interaction between groups and time was significant (F = 38.87, df = 6/336, $p < 0.01$) (see Figure 6).

Biochemical Variables

The difference between the autistic children and the normal children for DA, HVA, NA, MHPG and VMA was examined for each biochemical variable using a two tailed Student t-test. Of these substances, HVA was significantly elevated in the autistic sample (t = 3.322, df = 35, $p < 0.01$). No other urinary neurochemical concentration was significantly different between experimental groups (see Table 1 and Figure 7).

Of the precursor-product ratios, significant differences between autistics and normals were found for DA/HVA (t = 2.983, df = 35, $p < 0.01$) and NA/MHPG (t = 2.201, df = 35, $p < 0.05$). The DA/HVA ratio was lower in the autistics, and the NA/MHPG ratio was higher. The remaining precursor-product ratios did not approach significance (see Table 2 and Figure 8).

Table 1

Mean Concentrations of Urinary Catecholamines and Related Metabolites in Autistic and Matched Normal Children

	Neurochemical				
Group	NE	MHPG	VMA	DA	HVA*
Autistic	1.04	1.67	8.49	0.82	1.76
Normal	0.85	1.84	9.04	0.81	1.17

Note. Unit = mg/d

*$p < 0.01$

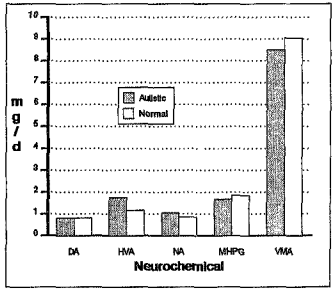

Figure 7. Urinary catecholamine concentrations.

Table 2

Precursor-to-Product Ratios of Urinary Catecholamines in Autistic and Matched Normal Children

	Neurochemical				
Group	DA/HVA**	DA/NA	NA/MHPG*	NA/VMA	MHPG/VMA
Autistic	0.57	1.73	1.41	0.24	0.47
Normal	0.91	1.91	0.60	0.15	0.33

Note. Unit = mg/d

*p < 0.05; **p < 0.01

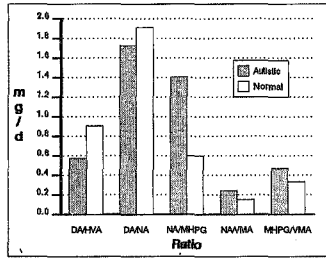

Figure 8. Ratios of catecholamine precursors to catecholamine products.

The ratio of HVA/CA was significantly higher in autistics (t = 3.065, df = 35, p = 0.01). The ratios of all other neurochemicals to CA were not significant. Nor was there any difference between autistics and normals for the total catecholamine synthesis (CA) (see Table 3 and Figure 9).

For the neurochemical variables that were significantly different between autistic and normal children (HVA, DA/HVA, NA/MHPG and HVA/CA), a Pearson correlation was calculated between these variables and the scores on the CARS. Correlations greater than 0.3 and less than -0.3 were deemed to be of sufficient magnitude to warrant reporting. Only three correlations met this criterion. For HVA and item 14 of the CARS (activity level) r = -0.34. For HVA/CA and item 14 the correlation was -0.46, and for HVA/CA and item 1 (relating to people) r = -0.39.

Table 3

Ratios of Urinary Catecholamines and Metabolites to Total Catecholamine Synthesis in Autistics and Matched Controls

	Neurochemical					
Group	DA/CA	HVA/CA*	NA/CA	VMA/CA	MHPG/CA	CA
Autistic	7.25	0.16	9.50	0.52	0.15	13.78
Normal	7.81	0.10	7.44	0.59	0.16	14.32

Note. Unit = mg/d

*$p < 0.01$

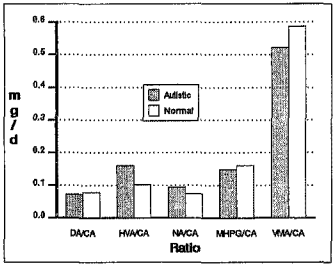

Figure 9. Ratios of individual neurochemicals to total catecholamine synthesis.

Cardiac-Biochemical Interactions

The differences between the autistic children and the normal children on the cardiac variables were regressed against the differences between groups on the biochemical measures, using a forward stepwise multiple regression. These interactions were only significant for trial one of the experiment; for other trials the interactions were not significant. Presentation of the first auditory stimulus (trial one) occured during seconds three and four of the experiment.

The correlation between the difference in HVA values and differences in cardiac activity during trial one was $r = 0.38$. The difference between groups was significantly predicted by HVA difference scores ($R^2 = 0.14$, $F = 4.50$, $df = 1/27$, $p < 0.05$). No significant predictive relationship existed for differences between the remaining catecholamines and related compounds (NA, MHPG, VMA and DA).

For the precursor-product ratio differences none of the regression relationships were significant.

The difference between ratios of individual neurochemicals to total catecholamine synthesis (CA) was significantly related to the difference between groups for cardiac activity during second four only. The highest correlation was for HVA/CA, which was $r = 0.53$. Regression

relationships were significant for HVA/CA (R^2 = 0.28, F = 10.36, df = 1/27, $p < 0.01$), NA/CA (R^2 = 0.36, F = 7.21, df = 2/26, $p < 0.01$), MHPG/CA (R^2 = 0.40, F = 5.62, df = 3/25), VMA/CA (R^2 = 0.43, F = 4.51, df = 4/24) and DA/CA (R^2 = 0.52, F = 5.03, df = 5/23, $p < 0.01$).

CHAPTER NINE -- DISCUSSION

In this study I measured the ECR of 29 autistic children and their age and sex matched normal controls, to a train of 15 auditory stimuli of moderate intensity. Urine samples from 36 autistic children and their controls were assayed by *HPLC* to determine the concentrations of the catecholamines NA, MHPG, VMA, DA and HVA.

The psychophysiological results demonstrated that attention was dysfunctional in autistics. This interpretation was consistent with the results of earlier psychophysiological studies into autonomic response patterns in autism (Cohen and Johnson, 1977; Condon, 1985; James and Barry, 1980, 1984; Kootz and Cohen, 1981; Kootz et al., 1982; Stevens and Gruzelier, 1984; Palkovitz and Wiesenfeld, 1980; van Engeland, 1984). The evoked cardiac response of the autistic children differed markedly from that of the normal children.

The neurochemical data confirmed existing evidence (Belmaker et al., 1978; Cohen et al., 1974, 1977; Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Israngkun et al., 1986; Lake et al., 1977; Lelord et al., 1977, 1982; Young et al., 1979) for a pathology in the *metabolism of catecholamines in autism*. A biochemical abnormality was demonstrated in both dopaminergic and noradrenergic neurotransmitter systems. The magnitude of the neurochemical metabolic disorder was greater in the

dopaminergic system, than in the noradrenergic system.

The relation between the biochemical and the psychophysiological data was examined. Statistical analysis indicated that the difference in attention between normal and autistic children, as measured by cardiac responsivity to stimulation, was predicted by the difference between the two experimental groups on measures of dopaminergic activity. However, this relationship held for the first trial only. The ECR difference between autistics and normals was greatest for the first trial, and diminished as the normal children habituated to the stimuli. This implied that the dopaminergic pathology contributed significantly to the attention dysfunction in autism, at the point where the difference between autistics and normals was greatest. On later trials, although the two groups differed in terms of their ECR, this difference was not attributable to the dopaminergic differences between the groups.

Thus, the relationship between the psychophysiological data and the neurochemical data provided some insight into the issue of whether or not the biochemical basis of attention dysfunction in autism could be identified. However, it was clear that the dopaminergic abnormality was only a small part of the attention dysfunction in autism. Factors which contributed to the remaining variance in cardiac responsivity to stimulation were not identified, but appeared not to be related to neurochemical abnormality in autism.

I now turn to a more detailed discussion of the results of this study. I begin with a discussion of the psychophysiological results. Next the neurochemical data is discussed and compared to other studies. Finally, the relation between attention status and neurochemical functioning is analyzed, in the light of the experimental findings.

Psychophysiological Results

There are two relevant questions to be answered: 'How do the results obtained in this experiment compare to other research on evoked cardiac responses in autism?' and 'What do these results mean?'

Comparison with Other Research. To my knowledge only six studies (Cohen and Johnson, 1977; James and Barry, 1980, 1984; Kootz and Cohen, 1981; Kootz et al., 1982; Palkovitz and Wiesenfeld, 1980 -- reviewed in Chapter 3) have been done on the cardiovascular psychophysiology of autism, and of these, only two examined the ECR (James and Barry, 1984; Palkovitz and Wiesenfeld, 1980).

Mean heart rate did not differ significantly between the autistic and the normal children in this study. This result was in contrast to some studies which have documented elevated tonic heart rate in autistics (Cohen and Johnson, 1977; James and Barry, 1980, 1984; Kootz and Cohen, 1981; Kootz et al.,

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1982), but was consistent with Palkovitz and Wiesenfeld (1980), who found no difference between autistics and normals for mean heart rate.

The ECR profile for the normal children in this study showed the expected pattern of deceleration in response to stimulation, and gradual habituation of this evoked response with stimulus repetition. A different response pattern was found in the autistic children. They showed no cardiac deceleration, instead they showed a gradual increase in heart rate (see Figure 6). This pattern of response was similar to that reported by Palkovitz and Wiesenfeld (1980) for the condition in which they presented 500 Hz auditory stimuli to autistic children. It was different, however, to the response pattern reported by James and Barry (1984), who found that autistics exhibited greater deceleration in response to stimulation than either normal or retarded groups.

Although some studies have found that autistics failed to habituate (James and Barry, 1980; Palkovitz and Wiesenfeld, 1980), the ECR profile of the autistics in this study should not be compared to other studies on those terms. This is because the autistic children did not show either habituation or nonhabituation, since they failed to respond to the stimuli in the first place. A nonresponse cannot be said to habituate (Barry, 1986).

Interpretation of the ECR. Some authors (e.g. Cohen and Johnson, 1977; Kootz and Cohen, 1981) have suggested, on the basis of psychophysiological studies, that autistics display a tendency to reject stimulation. Caution should be exercised when interpreting autistics' ECR in terms of the intake/rejection hypothesis (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970, 1974).

The failure of the autistic children to show a decelerator ECR may not be interpreted to mean that they tend to reject stimulation. The rejection of sensory information corresponds to an increase in heart rate (Lacey J.I., 1967; Lacey, J.I. and Lacey, B.C., 1970). Although heart rate did show a tendency to accelerate relative to baseline in the autistics, this change was not significantly different from baseline heart rate, and therefore probably reflected a tonic change in heart rate rather than the active phasic rejection of sensory stimulation. For the rejection hypothesis to be applied to the ECR profile, the acceleratory response should have been immediate and steep, and not as delayed and gradual as it was. At best, this result meant that autistics did not show the characteristic psychophysiological signs of the intake of information. It would be invalid to conclude that this was equivalent to the rejection of information.

The intake/rejection model of the Laceys (Lacey, B.C. and Lacey, J.I., 1980; Lacey J.I., 1967; Lacey, J.I. and Lacey,

B.C., 1970, 1974) does not provide a useful analytic tool in this instance. The nonresponse of the autistics does not fall neatly into their model. The Laceys assumed that sensory information processing will occur in response to stimulation, but this did not appear to hold for the autistics, who showed no signs of phasic autonomic responding (see Figure 6).

The lack of a decelerator ECR in autistic children may indicate a preattentive information processing pathology, along the lines of the model of orienting described by Ohman (1979). The ECR of the autistics lends support to the view that they have difficulty in orienting to stimuli, and interrupting ongoing cognitive activity in STM, as well as difficulty initiating central processing of incoming information, by the redistribution of processing capacity. The autistic ECR profile obtained in this study was indicative of a failure of this arousal based preattentive parallel process interrupt system. Either, there was no call for capacity in the central processor, when one should have been made, or the call, the interrupt, was made, but was unsuccessful. The differences in the ECRs showed reduced orienting among the autistics.

The nonresponse of the autistics may have been a result of a breakdown of the habituation bias. Alternatively, it may have resulted from a deficiency in the operation of the redundancy bias. Both possibilities are discussed below. The reciprocal relationship between habituation and redundancy

probably entails that a breakdown in either system will affect the other system *in some manner*, and that it may be incorrect to conceptualize the problem in autism as residing with only habituation or redundancy.

The lack of response in the autistics may be because no mismatch occured, and as a *result* no preattentive processing was initiated. A mismatch process deficit in the habituation bias controls on attention, would have the consequence that stimuli would not be identified as novel (or significant) by the autistics. A habituation bias dysfunction would make autistics more susceptible to noise in information channels, and less likely to orient to information, and produce a mismatch signal in response to novel stimuli. The ECR of the autistics may indicate the operation of precisely such a dysfunctional process.

The observed autonomic nonresponse of the autistics may have been the result of a deficient redundancy bias. The ECR profile of the autistics suggests that a redundancy bias may have been operative at the time of the experiment. This would have the result of making the autistic child nonresponsive, because the redundancy bias restricted the range of stimuli which the child would process. Under such conditions, many stimuli would be irrelevant because they failed to meet the criteria for the response set, as determined by the redundancy *bias*. The failure of the autistics to demonstrate a deceleratory cardiac response may be because the stimuli fell

outside the range of the redundancy bias. Whereas stimuli were processed as novel by the normal children, the same stimuli resulted in a nonresponse in the autistics.

The nonresponsiveness of the autistics may be because they were unable to inhibit existing neural patterns, and bring about a change in the focus of attention. Autistic children may be unable to orient to sensory stimuli, because they perseverate at the sensory level. They were unable to make the switch between one stimulus configuration (silence) and another (stimuli). Interrupting and overriding the existing response set appeared more difficult in the autistics. A problem of such a nature may stem directly from the operation of an redundancy bias, which under normal circumstances operates to restrict information change (Tucker and Williamson, 1984). If the redundancy bias is too powerful in autism, then change in the sensory response set may be made more difficult than normal. The obtained ECR profile suggested that this may have been the case.

It is interesting to speculate that if the severity of this dysfunction of attention in autism fluctuates temporally and spatially, then attention may be impaired more severely at one time, as compared to another, and may be more impaired for some types of stimuli than others. An attention dysfunction of variable temporal and spatial severity may explain the appearance of isolated areas of intact attention in autism, as evidenced by idiot savant autistic children (Restak, 1982).

During the final trail the frequency of the stimulus was halved. According to Sokolov's (1958, 1963) theory this should have had the effect of dishabituating the orienting response. In the normal children heart rate did decelerate at this point, although not to the extent that was predicted by Sokolov's theory. It has been speculated that ORs to changes in stimulus parameters of this sort represent voluntary responses and not involuntary reflexes (Maltzman, 1979). This may be why the magnitude of this response was not as great as for the onset of the stimulus train, in the normal children. If Maltzman is correct then this kind of voluntary orienting response was absent in autistics.

This experiment was designed to elicit an external control of information processing in attention. The stimuli were novel, and no other information processing demands were made on the children at the time of the experiment. In the normal children, attention was brought under external control by the stimuli, as predicted by theory and shown by their orienting response. The nonresponse of the autistics may indicate that their attention remained under internal control, despite the experimental conditions. The autistic children appeared to be indifferent to stimulation, and this may be because their attention was under tight internal control of the redundancy bias.

Neurochemical Results

A clear difference was found between the autistic and the normal children on urinary measures of chemical activity of the dopaminergic system. There was also evidence of a noradrenergic involvement in autism.

Comparison with Other Research. In this study levels of urinary HVA were found to be significantly elevated in autistics. Of the six reported studies (Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Lelord et al., 1978, 1982; Minderaa et al., in press, cited in Anderson and Hoshino, 1987) which compared either urinary, plasma or CSF levels of HVA between normal and autistic groups, only one (Minderaa et al., cited in Anderson and Hoshino, 1987) found no difference between groups (for urine and plasma). The other five studies found that HVA levels were significantly elevated in autistics (Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Lelord et al., 1978, 1982).

None of the reported studies examined the ratios of precursors to products, or the ratios of individual neurochemicals to total catecholamine synthesis, as was done in this report, and therefore no comparison was possible. I found that the ratio of DA/HVA was decreased, and HVA/CA was increased.

Only Minderaa et al. (cited in Anderson and Hoshino,

1987) have examined DA directly, and they found, as I did, that there was no difference between autistics and normals for urinary DA.

No studies have examined the ratio of urinary NA/MHPG in autism. I found this ratio was increased in autistics. Plasma NA has been found to be elevated in autistics (Israngkun et al., 1986; Leke et al., 1977). Urinary MHPG was decreased in the autistics studied by Young et al. (1977), but concentrations were unchanged in the present study. CSF MHPG was unchanged in the Gillberg et al. (1983) and Gillberg and Svennerholm (1987) studies.

Interpretation of the Neurochemical Data. The elevated levels of HVA indicated that dopaminergic turnover was increased in autism. The same conclusion was supported by the decrease in the precursor-product ratio of DA/HVA in autism. The increase in the ratio of HVA/CA in autistics indicated that DA turnover is increased, relative to the concentrations of all catecholamines.

The increase in the ratio of NA/MHPG indicated that the turnover of NA was decreased in autism. The NA/MHPG difference was not as marked as the difference in dopaminergic transmission between the two groups. This was indicated by the nonsignificance of the difference in MHPG concentrations between autistics and normals, whereas the corresponding dopaminergic metabolite, HVA, was significantly different between groups. Further, the value of p was 0.01 for the

DA/HVA precursor-product ratio, but p was only 0.05 for the NA/MHPG precursor-product ratio.

These results confirmed other reports which have indicated that catecholamine metabolism was pathological in autism (Belmaker et al., 1978; Cohen et al., 1974, 1977; Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Israngkun et al., 1986; Lake et al., 1977; Lelord et al., 1977, 1982, Young et al., 1979). It follows that those anatomical regions of the brain which have been shown to contain catecholamines (reviewed in ~ are implicated in the pathology of autism.

The finding of a dopaminergic pathology in aut... is consistent with models of mental disorders which place an emphasis on the role of DA in the etiology of these syndromes (Crow et al., 1978; Julien, 1981; Swerdlow and Koob, 1987). Clearly, earlier studies which found DA abnormalities in autism (Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Lelord et al., 1978, 1982), are also consistent with dopaminergic models of mental illness.

Models of dopaminergic pathology in mental illness were once specific to schizophrenia (Crow et al., 1978). However, the model proposed by Swerdlow and Koob (1987) postulated that a DA disorder underlies a variety of mental illnesses, including schizophrenia, mania and depression. This broadening of the spectrum of disorders to which the DA model of mental illness is applicable reflects a new approach to the

relation between neuropsychiatric disorders and brain dysfunction:

> The goal of this approach is not to understand the etiology of a single disease, but rather to study how dysfunction in a single brain system contributes to similar behavioural abnormalities in different disease processes. (Swerdlow and Koob, 1987, p. 202)

I have already discussed the brain system to which Swerdlow and Koob (1987) refer: the mesolimbic and mesocortical dopaminergic systems centred on a cortico-striato-pallido- thalamic loop.

Thus, if the Swerdlow and Koob (1987) model is correct, then the brain regions implicated in autism may be narrowed down from areas containing catecholamines, to mesolimbic and mesocortical dopaminergic systems. On the basis of research done on the brains of autistics (DeLong, 1979; Gaffney et al., 1987; Bauman and Kemper, 1985 -- reviewed in Chapter 4) it reasonable to conclude that mesolimbic and mesocortical DA may be dysfunctional in autism.

The Neurochemistry of Attention in Autism

The fact that an attention dysfunction and a neurochemical pathology were found in the same autistic children suggested that these deficits were related in some way. Nevertheless, co-occurrence is not evidence for interaction, nor causation.

The stepwise multiple regression showed that some of the variance in attention may be accounted for by the chemical difference between autistic and normal children. This meant that the attention dysfunction was related to neurochemical status in autism.

As I have I have noted above, the regression was only significant for the first trial. Thus only when the difference in attention between normal and autistic children was at its most extreme, did the neurochemical difference between the two groups contribute to the attention dysfunction in the autistics. This meant that there were other factors involved in the attention dysfunction in autistics. The attention dysfunction cannot be explained solely by reference to the neurochemical differences between autistic and normal children. Nevertheless, the attention dysfunction was related to the neurochemical pathology. There does appear to be a connection between attention and neurochemistry.

I found that of the biochemicals assayed, HVA values regressed significantly on the cardiac values, during the first trial. The ratios that included total catecholamine synthesis in the denominator were all significantly related to cardiac responsivity. There were two characteristics to this data (a) the relation between HVA and attention and, (b) the relation between total catecholamine synthesis and attention. The HVA related data indicated that differences in the turnover of dopamine between autistic and normal children,

contributed significantly to the variance in the autistics' ECR during the first trial. The regression data showed no specific noradrenergic involvement. Differences in attention were also related to total catecholamine synthesis, indicating that differences in the overall pattern of catecholamine metabolism contribute to differences in attention between autistic and normal children.

Central vs. Peripheral Issues. It is appropriate to digress briefly at this point to discuss an issue which may be taken to proscribe linking attention and neurochemicals on the basis of the data obtained in this study. Since a major component of attention involves neurochemical functioning within the CNS, rather than the peripheral nervous system, the extent to which the urinary neurochemicals assayed in this study reflect CNS activity is of relevance.

VMA is known to be largely of peripheral origin (Cooper et al, 1978), and was studied here only because the assay procedure returned values for VMA, in addition to the neurochemicals of interest. The proportion of DA and NA in urine that is of central origin is unknown. Until recently DA and NA could not be detected outside the blood-brain barrier (Cooper et al., 1978). However, the development of more sensitive techniques, such as HPLC, the detection of DA and NA in plasma and urine has been possible. Estimates of the percentage of urinary MHPG of central origin have ranged from 20% (Blombery, Kopin, Gordon, Markey and Ebert, 1980) to 60%

(Raskin et al., 1984; Shaywitz et al., 1983). Central DA functioning appears to be reliably indexed by urinary HVA, as destruction of central DA neurons by 6-OHDA, causes a marked decrease in levels of urinary HVA (Peyrin, Simon, Cottet-Eymard, Bruneau and LeMoal, 1982). Some 72% of urinary HVA has been shown to be of central origin (Peyrin et al.).

The fact that not all the neurochemicals found in urine are of central origin, must be borne in mind when evaluating the results obtained in this research. However, it is not an issue of critical methodological import, although it would be interesting to know how using CSF measures instead of urine, would have changed the pattern of the results. Nevertheless, the catecholamine most clearly implicated in autism in this study was HVA, and urinary HVA appears to be a good index of central DA functioning (Peyrin et al., 1982). Furthermore, it should be remembered that attention is not solely CNS function, as skin conductance, electrocardiograms, electromyograms and other psychophysiological measures so aptly demonstrate: attention has identifiable autonomic components. Thus, including both peripheral and central measures of neurochemical functioning may be appropriate when discussing attention.

Catacholamines and Attention. The finding that during trial one, evoked cardiac responses were related to HVA levels, provided evidence that dopaminergic metabolic

pathology, rather than noradrenergic pathology, was related to orienting response dysfunction in autism.

The theory of the neurochemical basis of attention originally advanced by McGuinness and Pribram (1980) and then revised by Tucker and Williamson (1984) predicted that a dysfunction of the orienting response would be related to a noradrenergic dysfunction. On that model, attention deficits of the sort found in autistics in this study would be caused by a NA involvement. In this respect, my data do not confirm the Tucker and Williamson model.

Tucker and Williamson (1984) are ambivalent about the role of DA in attention. On the one hand they imply DA is not directly involved in information processing:

> Although DA systems thus target motor functions, and do not appear to have the major role in sensory processes shown by NE, they do appear important to coordinating motor output with perceptual information. (Tucker and Williamson, 1984, p. 192).

This would seem to imply that DA is only indirectly involved in information processing via its role in coordinating perceptual data with motor behaviour. Here, its primary function is seen as modulating sequential, ordered, motor behaviours, and maintaining motor readiness, perhaps by influencing motivation via mesolimbic DA connections (Tucker and Williamson, 1984). On the other hand, Tucker and Williamson seem to suggest that DA has a highly significant

role in information processing:

> Although the immediate effect of a redundancy bias is to maintain constancy in attention, over a period of time a succession of attentional foci produce a differentiation of the stimulus array in specific elements. This differentiation of percepts or concepts may reflect a higher order capacity... that *depends on* the... elementary control of a redundancy bias. (Tucker and Williamson, 1984, p. 205)

This suggests a different perspective on the role of DA in attention, implying that DA may be intimately involved in information processing. *It is difficult to reconcile* the DA findings of this study with the former view of DA in attention. However, the latter view may provide a *useful* means of understanding the role of DA in attention dysfunction in autism.

The direct involvement of DA in attention has been shown by animal studies (e.g. Chiodo et al., 1980; Crider et al., 1982, 1986; Fink and Smith, 1980; Simon et al., 1980 -- reviewed in Chapter 6), and by human clinical groups with attention deficit disorders, and corresponding DA deficiencies (e.g. Raskin et al., 1984; Shaywitz et al., 1983). These data support the view that information processing is directly affected by a dopaminergic mechanism.

As I have noted above, the nonresponse of the autistics may be related to a breakdown in the normal habituation bias

control on attention, or it may be related to a malfunction in the redundancy bias control. Following Tucker and Williamson (1984), a habituation bias deficit implies a noradrenergic pathology, and a redundancy bias dysfunction a dopaminergic deficiency.

The neurochemical data obtained from the autistic children suggested a diminished NA turnover rate. The consequence of an impairment of the habituation bias through low NA turnover, might be that novel input is attenuated, instead of being processed. If this is so in the autistics, then it is consistent with their ECR profile. The decrease in NA turnover indicated by the increased NA/MHPG ratio in autism, may be responsible for an attention deficit in autism which takes the form of diminished responsivity to novel input.

This view was not supported by the multiple regression analysis, which indicated that neither NA/MHPG, NA, nor MHPG were predictors of attention dysfunction. Thus, although a noradrenergic pathology was found in the autistics, it does not appear to be related to the observed attention dysfunction.

The results obtained from the autistic children may be interpreted in terms of Tucker and Williamson's (1984) construct of redundancy. The finding of dopaminergic abnormalities in autism in this study lent support to this view, and the regression indicated that DA and attention were

related in the autistics, at least for the first trial.

If the redundancy bias is dysfunctional in autistics, then they would be less responsive to information. An overactive dopaminergic based redundancy bias would make most information irrelevant. The autistic would become overselective. This may explain the cardiac nonresponse of the autistics to stimulation.

According to Pavlov (1927, 1928) the 'What is it?' response precedes the 'What is to be done?' response; arousal precedes activation (*Pribram and McGuiness*, 1975); habituation biases operate before redundancy biases (Tucker and *Williamson*, 1984). If autism is characterized by the operation of a redundancy bias on information flow in attention, this may explain the delays reported in brainstem transmission time (Fein et al., 1981; Tanguay et al., 1982; Gillberg et al., 1983), as well as delayed skin conductance response latencies in autism (Stevens and Gruzelier, 1984). The operation of the redundancy bias may explain the appearance of late slow waves in the autistic evoked response potential (Lelord et al., 1973; Martineau et al., 1980). Since the operation of redundancy requires retrieval of information from long term memory and cognitive processing, the deviance in P300 peaks in autism (*Courchesne et al., 1984, 1985b*; Pritchard et al., 1987; Niwa et al., 1983) may be due to the *redundancy bias*.

It should be noted that dopamine turnover increases

tremendously with motor activity (Freed, 1986). Since autistic children are often hyperactive, it might be objected that the DA measures obtained in this study index motor activity, rather than any other alleged sensory attention related properties of the DA. However, since the urine samples obtained from the children were all early morning samples, they were relatively free from any compounding effects of movement, and therefore may index "nonmovement" related DA.

The function of DA may be to order and structure information flow by limiting its turnover rate, and restricting the input of new information (Everts and Wise, 1984; Marsden, 1984; Tucker and Williamson, 1984). This is consistent with the role of DA in both motor and sensory control. If the redundancy bias was increased in a motor channel by elevated DA, then the result would be behavioural stereotypies (Dickinson and Curson, 1983; Iversen and Iversen, 1975). This is consistent with the presenting symptoms of autistic children. Stereotypies, such as hand flapping and rocking back and forth, are one of the hallmarks of autistic behaviour.

What would the effect of increased DA turnover be on attention in autistics? Under normal metabolic conditions, DA may assist in promoting a focused mode of attention. However, this may change when DA metabolism is pathologically elevated, as in the case of the autistics. Rats with increased DA

turnover showed diminished interest in novel stimuli (Fink and Smith, 1980). Selective attention was impaired in rats treated with amphetamine, and these animals showed an inability to filter out irrelevant stimuli (Crider et al., 1982, 1986). The autistic children in this study showed similar changes in responsivity, as indicated by their failure to orient to novel stimuli. Thus the attention dysfunction in the autistic children may be directly related to their increased DA turnover rate.

These changes in attention may be related to arousal. This would be consistent with Iversen and Iversen (1975) who postulated that nonresponse in 6-OHDA treated animals to stimulation may be related to the role of DA in arousal. It is also consistent with Hutt et al.'s (1964) suggestion that autistics are hyperaroused.

The effect of elevated DA on sensory attention may also be related to the role of DA in effort. It will be recalled that whereas McGuiness and Pribram (1980) allocated the effort construct in their model of attention to peptide controls, Tucker and Williamson (1984) included effort in the domain of DA, and not peptides. Effort is important in the control the organism has in exiting from stimulus-response loops (Pribram and McGuiness, 1975).

The motor stereotypies that result from elevated DA (Dickinson and Curson, 1983; Iversen and Iversen, 1975) may have an analogue in attention in autistics. This may take the

form of sensory perseveration. The perseveration of attention may result from a failure of the effort system to exit the autistic's attention from a sensorimotor response loop. The autistics did not appear to be able to respond to the information properties of new stimuli, because they may have been unable to exit the stimulus-response loop that was current, and refocus their attention on incoming stimuli. Since effort is a higher order construct, and involves voluntary processes, as opposed to involuntary processes such as activation, the failure of the autistics to respond to stimulation may be related to a motivational deficiency in autism. This is consistent with the role of DA in motivation (Panksepp, 1986; Stein, 1978).

Sensory perseveration in autism may also result from the operation of the redundancy bias. As I have noted, the effect of a redundancy bias is to restrict information change, and impose order on sensory processing. A redundancy bias that was malfunctional would result in an abnormally tight restriction on information processing. The rate of change in the information channels would be minimal. In this sense, a redundancy bias that was overactive would cause perseveration at a sensory attention level. This may be part of the mechanism involved in the attention dysfunction observed in the autistics. Their attention may be overwhelmed by the redundancy bias, and this may explain their unresponsiveness to stimulation.

The dopaminergic involvement in autism, as found by this study and others (Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Lelord et al., 1978, 1982), and the link between attention dysfunction and dopaminergic measures, support the view that 'cognitive style' in autistics shows a high degree of internal control. This is a consequence of the redundancy bias. From this it follows that the scope of the representation of the external environment is constricted in autism. The 'beam of the spotlight' of attention is narrowed in autism. An internal locus of information control corresponds to a cognitive style in which past representations tend to control information flow, more than new incoming data.

Implications for Future Research

Improvements. This study could be improved by being repeated with more control groups. If controls were matched for mental age and chronological age (Yule, 1979), then the extent to which mental retardation contributes to these findings in autistics could be gauged. The confounding effect of mental retardation might also be lessened if only high functioning autistics were used in future studies.

Urine is a relatively inexact measure of CNS catecholamine activity. Future studies could, if ethical considerations permit, use CSF instead of urine. A wider

range of neurochemicals could also be assayed, since evidence suggests that opiod peptides (Gillberg et al., 1982, 1985; Israngkun et al., 1986) and serotonin (Anderson and Hoshino, 1987; August et al., 1984) may be involved in the pathogenesis of autism.

In this study attention was assessed under very straight forward conditions. However, responses to a train of simple auditory stimuli provide a limited amount of information about attention. Other tasks could be included in the experimental paradigm of future research. In particular, the blocking paradigm of Crider et al. (1986) would provide for an interesting and informative assessment of attention in autism. Tasks could also be designed on which success demands the appropriate application of the habituation and redundancy biases. A more exact test of habituation and redundancy in autism would help illuminate the nature of the attention dysfunction in autism.

Extensions. The results of these experiments implied that the redundancy bias is weighted too high in autistics. In terms of the remediation of autistic symptomology a few alternatives suggest themselves. Firstly, redundancy may be present in autistics in their motor stereotypies. An *occupational therapy programme could be developed to attempt* to extinguish the repetitive behaviours. Secondly, since redundancy implies that new stimuli are likely to be rejected in favour of reprocessing existing stimuli, attention training

tasks could be developed which emphasize creative responses to novel stimuli. Tasks could be designed which reward orienting to novelty.

Thirdly, and much more difficult, would be the institution of a programme to activate effort in autistics. It is not clear to me how autistics could be motivated.

Conclusion

The results of this study confirmed the findings of earlier studies into the neurochemistry of autism, which found that dopaminergic metabolism was elevated (Garnier et al., 1986; Gillberg et al., 1983; Gillberg and Svennerholm, 1987; Lelord et al., 1978, 1982). Somewhat unexpected, was the result that showed that noradrenergic metabolism was decreased in autism. This was consistent with the finding that dopamine-ß- hydroxylase levels were decreased in autistics (Lake et al., 1977), as were urinary MHPG levels (Young et al., 1979).

On the basis of the psychophysiological findings of this study it may be concluded that attention in autism is dysfunctional. Of the two studies that have examined the evoked cardiac response in autism, one (James and Barry, 1984) found that heart rate deceleration in response to stimulation was greater in autistics than normals. The other (Palkovitz and Wiesenfeld, 1980) found that autistics showed no

deceleration in response to auditory stimulation, and this is consistent with the results of this study.

The absence of a decelerator cardiac response in the autistics represented the breakdown of the orienting response, and the setting aside of processing capacity in short term memory (Ohman, 1979), as well as the failure of the autistics to voluntarily process novel stimuli (Maltzman, 1979).

One of the key issues in this study was whether the biochemical basis of attention dysfunction in autism could be identified. This study contributed towards that goal. Dopaminergic abnormalities were shown to be significantly related to the failure of the autistics to orient to the stimuli. Thus DA is part of the neurochemical substrate of attention dysfunction in autism.

The attention dysfunction in autism may be interpreted to depend on the malfunctioning of a redundancy bias. This bias is one of the normal mechanisms that allow for the selfregulation of attention in response to environmental demands (Tucker and Williamson, 1984; Wickens, 1984). The operation of the redundancy bias has been shown to depend on dopaminergic functioning (Tucker and Williamson). The elevated levels of dopamine in autism may therefore load the redundancy bias to reject incoming information as irrelevant, and minimize orienting behaviour.

The overactivation of the redundancy bias by elevated dopamine turnover may cause attention to perseverate in

sensorimotor response sets in the autistic's consciousness. The perseveration *in attention produced* by DA excess, parallels the perseveration in motor behaviour caused by increased DA turnover, and *manifested as stereotypies*. The role of DA in attention is supported by animal studies, which showed that selective attention deficits can *be induced in* experimental animals by the manipulation of DA metabolism (Crider et al., 1982, 1986; Fink and Smith, 1980; Simon et al., 1980). A DA mechanism in attention is also indicated by other clinical groups that present with both DA abnormalities and attention dysfunction (Raskin et al., 1984; Shaywitz et al, 1983).

A dysfunction of attention in autism is also indicated by the congruence of brain areas implicated in attention (Khomskaia, 1972/1982; Pribram and McGuiness, 1975; McGuiness and Pribram, 1980) and brain regions found to show signs of pathology in autism (Bauman and Kemper, 1985; DeLong, 1979; Gaffney et al., 1987). Brain regions rich in catecholamines also show an overlap with areas involved in attention, and implicated in autism. Since the catecholamines are implicated *in attention* (McGuiness and Pribram, 1980; Panksepp, 1986; Tucker and Williamson, 1984), this lends support to the view that *attention dysfunction* in autism is related to dopaminergic abnormalities.

Dopamine pathology is believed to be common to a variety of mental illnesses, and is thought to center on a common

dysfunction in information processing in a series of neuronal loops centered on the cortico-striato-pallido-thalamic regions of the brain (Swerdlow and Koob, 1987). Autism may be one of the syndromes accounted for by this model.

The cognitive style of the autistics shows a tight internal control over all stimuli that are processed. Instead of orienting normally to stimulation, the autistic children appeared not to respond, as was shown by their cardiac response profile. This nonresponse may be related to a cognitive style in which the representational scope of attention is narrowed, and only stimuli which are relevant because of past associations are processed. This distinction between internal and external factors in cognition appears to identify important factors in the breakdown of cognitive processes because of biological abnormalities, and features in two models of biological basis of information processing: Tariot and Weingartner (1986), and Tucker and Williamson (1984).

Relating cognitive style to physiological parameters is in essence an extension of the programme embarked on by Pavlov (1927, 1928). Autistic consciousness may be characterized as tightly bound to the internal control of perseverating sensorimotor stimulus-response sets in attention by an overactive dopaminergic redundancy bias.

CHAPTER TEN - REFERENCES

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