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FOREWORD

AD/HD - On thirteen ways forward

"Has this child a problem?", asks a parent, a teacher, a health professional. Most would anticipate a black-and-white answer. A categorical yes or no. If "yes", then the nature of the problem is clearly one that requires the attention of a professional therapist. The observer may perceive and describe the potential problem as being one of 'Cannot sit still or concentrate', 'impulsivity', 'poor control of behaviour and emotional responses'. Through observation, an interview and psychometric testing the professional now has to decide if 'attention is impaired', 'response inhibition is poor' and so on. S/he will do more, of course, but these are all helpful and necessary for making a diagnosis and designing an appropriate form of help.

This sounds to be, often is and certainly has long been a categorical decision. The medical establishment requires that a certain number of features must be ticked off when concluding with a diagnosis. However, there is now recognition, not only that this is not really the way we make such decisions (Is the child *more* restless than I might expect a 6 year-old to be? How much more?). It sounds reasonable that our observations should be formalised by rating the degrees of severity of the problem feature(s). Is there a little, a modest amount or quite alot of the item concerned? But note that this implies recognition that the item itself can be found in all 6 y-olds. The question is the degree to which, in the present case, there is rather alot or just a little of it present.

This is a dimensional approach. This recognises that activity and attentional impairments are found, more or less, throughout the population. Does the degree of expression come at one or the other extreme of the inverted U-like curve showing a normal distribution of the item in 6 y-olds? This is the question, indeed the message that *Wai Chen and Eric Taylor* wish to put across in the opening chapter of the current collection. A very good reason for using the dimensional rating approach that they advocate is to provide a much needed alternative to the categorical diagnoses provided by the World Health Organization and the American Psychiatric Association.[1] The significance of the dimensional approach may be found through

[1] Note the paradoxes: The *I*nternational *C*lassification of *D*iseases (ICD) from the WHO requires the presence of the symptom "inattention" for a disorder formally known as the *h*yper*k*inetic *s*yndrome (HKS); the *D*iagnostic and *S*tatistical *M*anual (DSM) from the APA allows for the determining of an overactive-impulsive sub-group without inattention for the diagnosis of *a*ttention-*d*eficit *h*yperactivity *d*isorder (AD/HD). This has contributed to some wildly different estimates of the prevalence of purportedly the same syndrome (Taylor, 1998). Recent

the messages of many of the succeding chapters, - not least because it has relevance for the way we assess the partial contribution of a number of the child's genes to the expression of the problem features (i.e., "polygenic contributions"). The authors trace the development of the interview known as the parental assessment of childhood symptoms (PACS) that culminates currently in a multicentre genetic research programme to study the various loci on the genome that contribute quantitatively (more or less) to one of the traits or problems under study.[2] This chapter provides an illuminating insight in to how to ask questions of informants, be they the affected children or the long-suffering parents, and how to weigh the answers. It has been and will be even more widely used in the future – a 'way forward' for research in this field.

To a degree, cases of AD/HD seem to group together within families. There is nearly a 5-fold increased likelihood of close relatives of a child with AD/HD also showing similar symptoms (Willcutt, 2005). To be sure, some of this may be acquired through the mere proximity of sharing the family environment. However, current work (the IMAGE study[2]) show that the probability of occurrence of a problem feature in one child occurring in a second child is at least as strong as that for features shared by dizygotic twins (Asherson et al., 2004; Kuntsi et al., 2005; Kuntsi & Asherson, 2005).

This leads us on to the range of approaches being mobilised to determine the "what" (feature) and "where" (chromosomal locus) in genetic research into the bases underlying AD/HD. *Florence Levy* working with colleagues from Australia and The Netherlands (Chapter 2) guides us into and through one of the minefields of classifying the types of cases the clinician sees and making this relevant to studies of the genetic bases (or helping to point to the environmental triggers). The diagnostic process is made complicated by the frequent co-morbidity of AD/HD symptoms with those of oppositional or conduct disorder. The authors make a quasi-link with the dimensional approach described in the first chapter by subclassifying conduct disorder into 3 sub-groups most easily defined by the dimension of severity of the type of symptoms shown. They have then looked for associations with the inattentive and hyperactive-impulsive subgroups of AD/HD within more than 500 mono- and di-zygotic twins who are part of a large register in Australia. Their first principle finding is that extreme conduct disorder characterised by conscious intentions to harm people, animals or property should be viewed as having quite separate and environmental causative agents. Their second finding is that there is a strong genetic effect underlying the two AD/HD subgroups, but that what they have in common with mild-moderate levels of conduct disorder is best explained by including environmental considerations. This provides a very important basis from which to proceed to look for commonalities at the genetic level, for the main features of the cognitive phenotype and as a guide for the direction in which would-be therapies should drive.

In Chapter 3 *Susann Friedel, Johannes Hebebrand* and colleagues introduce us to some of the 'hows', 'whens', 'ifs' and 'buts' that are part of the daily bread of genetics researchers. This is very useful for those working in different if related fields. Their account articulates the general methods, and assumptions that, for many, are easily overlooked and sometimes difficult to express. Not least among the caveats enumerated they urge care in comparing the

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conservative estimates from the UK suggest a prevalence of 1% for DSM-IV combined subtype (Ford et al., 2003).

[2] This approach to linkage and association mapping is known as the *Q*uantitative *T*rait *L*ocus paradigm (QTL) and is being practised in the *I*nternational *M*ulticenter *A*DHD *Ge*netic study (IMAGE)

different sources of our information (the raters), and remind us that the powerful evidence for a strong hereditary component in AD/HD also informs us that the so-called sub-forms of the disorder do not 'breed true'. This could be taken as further support for the dimensional and quantitative trait approach, as well as the need for more research. But it also reminds us that the search for an endophenotype for cognitive or motor functions is not just in its early stages, but that the concept itself needs refining: there remain elements for the argument that there is no endophenotype (a categorical function) in the usual sense of its use. In the broad sense the search goes on: twin data show that executive and alerting (and not orientation) components of attention and cognition have a degree of heritability (MZ *vs*. DZ twins - Fan et al., 2001). But what about the narrower sense of the concept pertaining to a person's specific capability?

What is the current consensus on features of AD/HD subjects that have a genetic basis? Chapter 3 convinces that the most robust finding in AD/HD is the association of a variable number tandem repeat (VNTR) polymorphism in exon 3 of the dopamine receptor D4 gene (*DRD4*). This is important as it is the D4 site (not the D2 or D3 site) that is responsible for the hyperactivity in the well-known dopamine-lesioned animal model of hyperactivity (Breese et al., 2005): the 7-repeat allele appears to be associated with an inaccurate, impulsive response style on neuropsychological tasks (Langley et al., 2004) and predicts response to ritalin therapy (Hamarman et al., 2004). More surprising is that this chapter introduces us to some doubts about the other strong candidate, the dopamine transporter (DAT1). The strength of the argument lies in the transporter being a likely target for the psychostimulants and that evidence for its involvement comes from quite separate genetic paradigms. But doubts must be raised following a meta-analysis of the first 13 studies. This claims that there is no effect: that the DA transporter gene (at least the 10-repeat allele) has little influence on the genetic susceptibility to AD/HD (Purper-Ouakilet al., 2005). In this chapter we also learn that the jury is still out on what influential feature of either the NA or 5-HT system is genetically determined and responsible for the undoubted partial contribution of the activity of these monoamines to the clinical picture of AD/HD. For serotonin, the transporter (see this chapter) is one possibility, but other loci (e.g. 5-HT1b) are proving of interest (Faraone et al., 2004; Li et al., 2005), and for noradrenaline evidence suggests that the involvement of the transporter is less likely than for a role for the alpha-2 family of receptors (cf. chapter 6, below, and De Luca et al., 2004; Park et al., 2004).

There is an, upto now, unspoken problem in these fields of genetic research. Do the existence of features and problems of perception and responsiveness, normally categorized under the name of another syndrome, also affect the phenomenon when seen in the separate syndrome under study? One aspect of this question is reflected in the overlap of genetic contributions to ADHD, autism and dyslexia touched on in chapter 3; another aspect of the question is touched on in the following chapter. This concerns the contribution of culture to the expression of symptoms.

What do we know about AD/HD in different lands, in societies not dominated by the 'Western' culture such as are found in South America, Asia and Africa? Certainly problems among Han Chinese and from the Colombian highlands are entering the general consciousness through certain well-publicised genetic studies. But Africa? We are indebted to the co-operation of *Anneke Meyer and Terje Sagvolden* in chapter 4 for opening our eyes to the situation among 6 ethnic groups in northern South Africa. In the first instance there was an epidemiological survey of over 6,000 children. It is not easy for non-Africans to imagine the difficulties of travel to these rural communities, of finding the appropriate care-giver,

informant and rater fluent in the language, and the collation of a full set of data. The astonishing outcome is that the cultural differences were so small that it proved unnecessary to develop ethnic-specific norms for the main dimensions of hyperactivity, impulsiveness and inattention. Prevalence was comparable to many western studies (5-6%) with nearly twice as many boys as girls affected. Neuropsychological tests of executive, coordination and motor function distinguished children with AD/HD from those without it, albeit with some variation with ethnic and gender grouping. The consequence is "yes" we are looking at a developmental disorder found worldwide, and "yes" we should always deal with the problems of an individual in that individual's specific context.

So given that everyone everywhere can expect to encounter the AD/HD phenomenon in their neighbourhood, we come to a series of 3 chapters aimed at relating aspects of research directed toward an understanding of how function and dysfunction in the monoamine neurotransmitter systems of the brain could give rise to the main features of AD/HD. Three points: first the material largely concerns the monoamine transmitters (dopamine DA, noradrenaline NA, adrenaline and serotonin 5-HT) known to be influenced by the succesful treatment of AD/HD children with psychostimulants. Secondly, these transmitters are also known to have a role in mediating some of the pertinent information processing mechanisms involved in attention, impulsivity, motor and stress processes. Thirdly I write, advisedly, on 'features' because the following two chapters are concerned with animals deliberately chosen to illustrate one or more isolated aspects either of monoamine dysfunction, or a classic example of an item from the AD/HD behavioural repertoire (i.e., a model).

The 'tour-de-force' from *Vivienne Russell* and her colleagues in Chapter 5 is a further example of Norwegian-South African cooperation. This is an extremely valuable resume of research activity with rodent models of AD/HD. A broad view over a range of animal models is laid out. This line of work all started in 1973, when a technique of administering the DA toxin 6-hydroxydopamine to the fluid spaces in the neonatal rat brain was introduced to selectively reduce brain DA levels. Rats became hyperactive as they grew up. As we now know with the help of specific pharmacological reagents and genetic studies, the DA D4 receptor had become hypersensitive (review: Breese et al., 2005). The evidence that the D4 site and its genetic basis seems pertinent to AD/HD is briefly reviewed in Chapter 3.

Russell's message is basically that we must consider the transport dynamics of DA in (and around) the synapse, but also the involvement of monoamines other than DA. For these authors and many others the spontaneously hypertensive rat (SHR) is the best rodent model we have, although some animals that have had the genes for specific receptors knocked out are useful for testing hypotheses for the role of substances binding to these sites. Advocacy for more studies of NA binding to the alpha-2a site and the role of NA activity here in information processing are well founded, and taken up in the following chapter by Amy Arnsten. However, because of the successes of the SHR in modeling several aspects of behavioural responsiveness and DA activity we must always bear in mind that it does not necessarily follow that the increased levels of NA, and decreased function of alpha-2a binding demonstrated in the SHR animal *necessarily* reflect the situation in a person with AD/HD. Indeed there is some reason to think that in these children NA activity may decrease (Chapter 7, Marat Uzbekov) especially if compared to DA function (Oades, 2002). Indeed, even with regard to DA function Russell accepts that the hyper-reactive rat model developed in Naples, accounts for some details of the syndrome more easily than the SHR (Oades et al., 2005). Part of the problem lies with agreeing on what is the best marker of the system's function or most

appropriate index of its activity. With regard to the other monoamines, the reader should not overlook the potential contribution of 5-HT activity to cognitive impulsivity reported for AD/HD children (Oades et al., 2002) and in the frontal regions of the rat (Dalley et al., 2002) simply because 5-HT activity in the SHR model is unremarkable (cf. review Oades 2005). Lastly, for those interested in the broader transmitter context, there is that other amine, acetylcholine. This should be mentioned in passing in view of changes in binding at several nicotinic and muscarinic sites in the SHR (Hernandez et al., 2003) and the therapeutic effect of nicotine in AD/HD.[3]

Amy Arnsten is especially concerned in Chapter 6 that we direct our attention to the role of NA in ADHD. In an all embracing tour from prefrontal cortical function in primates to the neurophysiological activity of NA neurons in the locus coeruleus, she reminds us of the excellent correspondence between the symptoms and neuropsychological problems of AD/HD. The picture she draws derives from both lesion and imaging studies of the prefrontal regions. Not least in her argument are the helpful effects of treatment with ritalin (methylphenidate) and other agents affecting noradrenergic transmission. Quite rightly she emphasizes the early descriptions from Steve Foote and colleagues (1975) on NA activity in tuning the signal to noise ratios in communicating neuronal networks, and the more recent demonstrations by Gary Aston-Jones and colleagues (Rajkowski et al., 2004) on how the interplay between phasic and tonic firing in NA systems promotes the processing of stimuli relevant to the situation in which an organism finds itself (early review in Oades, 1985). Work in Arnsten's own laboratory (e.g. Ma et al., 2003; 2005) is providing a fascinating story on how manipulating the alpha-2a receptor activity influences delay related responses in the prefrontal regions of monkeys, differentially influences the types of error the animals make during task performance and can even modulate motor responsiveness. There is much that echos observations of children with AD/HD. Some would put the emphasis on the stages of information processing being affected (cf. psychophysiology below), while Arnsten prefers to focus more specifically on the end effects, on working memory. The difference between these viewpoints relates to some of the dangers in naming the grander variables that intervene in cognitive processes: of these there are several that can be named, such as impulsiveness, working memory, inhibition, attention and filtering. More importantly for future research into how the mechanisms work, the question remains as to how one can manipulate NA levels appropriately for the right level of neural activation. Here the 'right level' depends on the affinities of the alpha-1, alpha-2 and beta receptor families in the different brain systems – that in turn affect, for example, stress as well as cognitive response. Happily this is the subject of much current study.

Chapters 7 and 8 consider the nature of the biochemical evidence for changes in the activity of monoamine systems in people with AD/HD. In different ways both chapters consider the signs that monoamine activity throughout the body is somewhat different in subjects with AD/HD. With due respect to the different metabolic pathways, peripheral measures of the overall somatic metabolism of these transmitters should, in the absence of other demonstrable disorders, reflect the minority contribution from the brain. But there should be no doubt that this signal is mixed up with much noise.

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[3] Acute and sub-chronic cutaneous administration of nicotine has been reported to reduce the variability of response on continuous performance tasks, and slow responding on Stroop- and Stop-tests as well as decreasing symptom severity (Levin et al., 2001; Potter and Newhouse, 2004). It may be noted that 'variability' is one of the key features of AD/HD.

Marat Uzbekov describes pilot work on the basic background levels of monoamine activity and explores if this could relate to symptom severity. His cases, explicitly diagnosed with the ICD system (hyperkinetic syndrome, HKS), showed that at rest there were rather small decreases of transmitter metabolites, while the precursors/parent amines could be excreted at higher (DA) or lower (NA) than normal levels. Although the rate of breakdown, catabolism (monoamine oxidase activity), seemed higher in the more severe cases, overall catecholamine turnover was reduced. Increasing severity was associated with even more DA synthesis and excretion of presumably unused transmitter. This implies hypofunction in the production of active transmitter. So, naturally one asks what happens under medication? In Russia a different type of psychostimulant is available for treatment: Sydnocarb. Its use not only ameliorated symptoms, but like other psychostimulants tended to decrease breakdown of the monoamines: it also decreased levels of monoamine oxidase. This sounds like a basis for amelioration of the children's problems. However, such measures are renowned for being exceptionally difficult to interpret.

Nonetheless, Marat Uzbekov goes on further to provoke the reader to pause and think. He has compared measures that contrast the rate at which the precursor tryptophan is metabolised either on the serotonin or the kynurenine metabolic pathway. He suggests the former may predominate in the untreated syndrome, while the latter is facilitated in those responding to medication. This is another way to view the claim of a hyper-function of serotonin in AD/HD (Oades 2002). In the spirit of this book it is another idea that should be tested to carry our understanding forward.

Chapter 7 also introduces a potentially very helpful animal model of AD/HD based on the foetal alcohol syndrome. This syndrome often ends up with a diagnosis of AD/HD (Hausknecht et al., 2005). The effect of alcohol on prenatal development is taken as an etiological model for the appearance of the syndrome (Taylor et al., 1998), allowing study of the biochemical concomitants in similarly treated animals. In the model prenatal alcohol should affect the performance of the progeny later on choice reaction time tasks, and prime the well documented symptoms of response time variability and increased rates of false alarms at times of choice. Indeed in the human condition prenatal experience with alcohol appears to moderate (exacerbate) the influence of the 10-repeat allele for the DA transporter (DAT1: Mill and Asherson cit. Stevenson et al., 2005) that is itself implicated in the characteristic of response variability (Bellgrove et al., 2005). Marat Uzbekov asks us to compare the similarities of measures taken from the children and the model. This divergent line of thought merits further investigation.

In Chapter 8 *Kerstin Konrad* reports a different approach with measurements from biological samples taken before and after a cognitive challenge. This 'challenge' - involving a small degree of activation and stress - concerned task performance indicative of abilities to sustain attention and to delay or withold responses. Like others before her, she finds that children with AD/HD do not show normal adaptive increases of adrenaline. This is related to poorer performance in terms of increased errors and lower signal-detection indices on the one hand and to ratings of impulsivity and inattentiveness on the other. It is difficult to know how to interpret the associations with 'pre-test' NMN levels, - where some report similar results and other do not. There is also a tendency for NMN to reflect extraneuronal metabolism. Indeed other NA metabolites (e.g., MHPG, DOPEG) are sometimes reported to be decreased, but to increase or normalise as the subjects grow up (Pick et al., 1999: review Oades, 2005).

The application here of eye-blink rates to indicate DA activity is surprisingly still relatively unusual, even though I find it useful for estimating whether psychotic patients are receiving appropriate doses of neuroleptics. Konrad confirms the broad impression of an overall hypo-dopaminergic system in AD/HD. The relationship of decreased blink rates with the difficulty to withold response is consistent with the difficulty to make paced changes of behaviour, - to 'switch', as it has been called in descriptions of the role of DA activity (Oades, 1985). It is useful that she relates these findings to Posner and Raichle's (1994) delineation of the central nervous networks of attention, - the adrenergic system is reflected in a fronto-parietal role in alerting, and the dopaminergic contribution is reflected in a medial frontal executive involvement in resolving conflict (an executive function).

Thus it is fitting that in chapter 9 with the help of *Sarah Durston* and her collaborators we come to consider what may be different among the major anatomical components of the brain. She, along with John Fossella and BJ Casey, remind us of the normal development of the brain, - a wide-ranging structural progression up to puberty followed by multiple regressive events thereafter, with mixed progression and regression continuing well in to what is normally considered to be young adulthood (the third decade of life). It is against this background that we must obtain the measure of neuroimages suggesting something different in AD/HD. For example, on the one hand brain volumes are reported to be slightly smaller in those with AD/HD – but this feature is non-progressive beyond about the age of 5y. Yet, over the next 10 years parts of the basal ganglia will decrease more in size in normal children, than those with AD/HD. In some situations AD/HD subjects may activate the frontal regions more, not less than normal as often reported (Vaidya et al., 1998: but see Bunge et al., 2002 for the differential involvements of the right hemisphere and ventrolateral regions): does this pattern arise because they need to mobilise more effort than normal children to meet a cognitive challenge, does this reflect a particular type of subject, such as those showing more theta *vs*. those with more beta EEG activity (see Chapter 13, below)? This is an exciting field throwing up answers that challenge our questions.

One approach described in chapter 9 is to "model" the potential developmental insult that could spark off neurobiological problems leading to AD/HD, namely with the study of children suffering an intraventricular haemorrhage (IVH). A series of behavioural and imaging findings are described that convince one of the need to indeed look closer. Are there comparable perinatal subclinical events in the history of children with AD/HD? A second approach involves the detailed comparison of twins discordant for the syndrome. It is widely appreciated that the right frontal regions conceal an AD/HD-related dysfunction: that this could be shared by affected and unaffected siblings alike points to an intriguing genetic lead: that it was the right cerebellar area that distinguished the affected siblings should lead to the re-orienting of some research programmes.[4] Their third example leads us in to the next chapter. What differences can one image when comparing children differing only in the gene determining the number of repeated transmembrane crossings found in the molecular structure of the DA D4 receptor? Sarah Durston reports that activation of prefrontal areas in a

[4] Relevant to the 'genetic leads' that this research is throwing up, I briefly mention one not discussed in this chapter (see Durston et al., 2004). The MR-anatomic finding is one of reduced substance in the right frontal and left occipital lobe in the ADHD sample. This should be seen in the context of normal brain development that leads to slightly larger right than left frontal and slightly larger left than right occipital lobe. This is known as torque. This is a classic feature for pursuit of genetic influences on development, as has been extensively discussed in studies of schizophrenia (e.g. Berlim et al., 2003)

Go/no-go task was more marked in those carrying the gene for 7 repeats than those carrying a set (homozygous) for 4 repeats. But does this mean that these children had to exert more effort (prefrontal activation) to perform the task or does the presence of the 7-repeat reflect a protective factor, as the authors propose?

Katya Rubia and associates report in Chapter 10 on a comparison of relatively large groups of children with AD/HD – half with and half without the 7-repeat genetic allele. Measures of impulsiveness included stop- and Go/no-go tasks as well as the ability to tap out certain rhythms. In their hands the 7-repeat group showed severer levels of cognitive impulsiveness and more variable motor responses than normal. This does not necessarily conflict with Sarah Durston's pilot work. Katya Rubia saw an indication that the children showing fewer than 7-repeats were the more inattentive subjects. Other work from this research group has often found abnormalities in the pattern of activation in the frontal lobes. The question then seems to revolve around other aspects of the phenotype shown, - inattentive *vs*. impulsive sub-groups, or other groups with/without abnormal theta/beta ratios of EEG oscillations (Chapter 13).

In chapter 11, *Anna Smith and Eric Taylor* look into an even more fundamental way in which subjects have been selected, sub-grouped and studied. Are clinically referred and non-clinical groups of children with AD/HD comparably impaired in their cognitive abilities (e.g. inhibitory abilities on the stop-task)? Indeed if the impairments are comparable one may well ask why such children do not become referred and receive treatment? They report that while the two sets of children performed similarly and poorly according to several measures, nonetheless a function reflecting their ability to inhibit responses showed the clinically referred subjects to be more impaired. In addition to the dimension of severity, referrals more often showed comorbid conduct disorder. So, on the one hand one can understand the basis for referral better, but on the other we perceive the grounds for a bias in the selection of groups often studied. We come nearly full cycle back to the the influence of comorbidity on our attempts to define the basic phenotype, as Florence Levy discussed in chapter 2.

In the last section we come to two techniques that directly register the neuronal responses of clusters of neurons in brains at rest, or engendered, challenged by carefully measured doses of relevant and irrelevant sensory stimuli. *Bob Barry* and his associates (Chapter 12) open a window on this line of research using electroencephalographic (EEG) techniques. Averaging the continuous records from the skull with respect to the time of stimulus presentation reveals positive (inhibitory) and negative (excitatory) responses over different parts of the cortices reflecting the stages of processing the stimulation. This Australian group provides a very useful introduction to work in this field showing that a number of very early stages of processing appear to run quite normally in children with AD/HD, until somewhere between one and two tenths of a second after presentation (see also Barry et al., 2003). Thereafter both inhibitory and excitatory processing runs anomalously. (In some situations difficulties are aleady seen at 100 ms post-stimulus.) They smoothe over a gap in our understanding of why this can in detail look a bit different for the visual and auditory systems, but indirectly acknowledge the problem by presenting novel data from a cross-modal paradigm.

They present an auditory target against an extramodal irrelevant visual context, providing noise to be ignored. They contrasted children with characters of the inattentive subtype and of the combined subtype of AD/HD. Common, as a core problem for both groups, was a reduction of the size of the P2 and P3 components. For the P3 this probably means a less effective update of the template that registers what has just happened, and for the P2 less use

of the neural capacity to promote channels for processing the target.[5] This relative inefficiency is reflected in what the authors call more equipotentiality (between electrode sites) of the response – a distributed but weak involvement of more regions of the brain. This is a feature also seen in neuroimaging studies of other psychiatric patients. Although all patients showed delayed component latencies, the inattentive group was especially variable and delayed, and additionally showed less initial enhancement of excitation by the stimulus (N1 component) in the right hemisphere. This is where others have noted reduced activity in undifferentiated AD/HD patients in neuroimaging of responses to task-relevant stimuli (Rubia et al., 1999) and deviant stimuli (mismatch negativity, Oades et al. 1996). The visual non-target stimuli unexpectedly showed reduced responsivity from as early as 50 ms to 250 ms (P1 to N2 components). Thus, remembering that the combined group may show inattentive features, but the inattentive group will be less hyperactive and impulsive, we can see a bias towards hypoarousal or inefficiency in the former, and towards immaturity of function in the latter.

The question of arousal and the so-called maturation lag is taken up again in Chapter 13 by *Adam Clarke* of the same Australian group. They measure the frequency of EEG oscillations topographically from the resting brain, and report on the proportion of slow and fast activity. In particular they emphasize the relative power in four frequency bands. In an exemplary introduction to the topic they show what are the characteristic features of young and not so young subjects with an AD/HD diagnosis (i.e., a high relative theta/beta ratio). They elaborate recent developments showing that there are clusters of subjects with different patterns exemplifying hypo-, hyper-arousal and a developmental delay (that may or may not mature later). Alas it was too much to hope that these clusters would match subtyping by classical DSM symptoms. However, in addition to being markers of arousability and perhaps maturation, these qEEG patterns over rostral and caudal parts of the scalp can be used as markers of medication response.

The report here describes what we understand about how firing frequencies in the brain predict the clinical responsivity to the psychostimulants methylphenidate and amphetamine. Quite novel here is the addition of information about the 20% or so of patients who do not respond well (or adversely) to psychostimulants. Who are they, and does imipramine help? The answer seems to be that a good response to imipramine can be expected in those with increased delta, reduced alpha and beta power over posterior sites – which is indicative of a maturation lag. This in turn reflects that the more hypo-aroused subjects are more likely to respond to psychostimulants. However, Adam Clarke reminds us that so long as we do not know how responders to the one psychostimulant would have responded to the other medications it remains equivocal what the precise characteristics of responders/non-responders are. The variability of the resting activity of children with AD/HD is large. It may well be, as with aspects of the psychopharmacological field of research, so in EEG investigations that studies using the response to perceptual or cognitive challenge will have to be assembled to appreciate the functional differences. This may be the ´way forward`. However, we should appreciate the ´current` situation where instead of pointing to the differences, one can illustrate the similarities of neurophysiological effect of agents that block

[5] As reviewed in this chapter, in paradigms that present several stimulus types within one modality impulsive responses are often acompanied by large P2 components interpreted as demonstrating the inhibition of processing of the information competing for processing capacity.

reuptake of the two catecholamines (methylphenidate), reuptake of the three monoamines (amphetamine) and "non-selective" re-uptake of noradrenaline and serotonin.

In conclusion, there is a dynamism among "current ideas" on AD/HD research which is extraordinarily encouraging as we look to the future and to the resolution of the problems of AD/HD. We can have more confidence than of late that we can determine and rate the problems grouped under the rubric of AD/HD (chapter 1), delineate them with respect to some prominent (if not all) related behavioural disruptions (chapter 2) and have some confidence in an inter-cultural commonality of a problem that may respond to attention from professional care-givers (chapter 4). We are standing already at the second stage of an understanding and attribution of genetic and environmentally mediated traits (chapter 3, 9 and 10): that the "way forward" (towards which feature(s) trigger(s) which effect(s)) may involve tens of stages is exciting - for the first results are at hand (e.g., DRD4). Which amine systems (DA, NA, 5-HT, adrenaline, acetylcholine) intervene with anomalous function is better understood qualitatively than quantitatively (chapters 5-8). Arguably this link in the chain of understanding has furthest to run, among the fields discussed in this book. What elements and features control the transport of a monoamine within and around the synapse and synaptic bouton (e.g., astrocyte metabolism, vesicle transporters, and neurexins), let alone the rules for extraneuronal uptake and release in neighbouring systems (e.g., DA by NA systems)? This knowledge will determine future generations of biologically based treatments.[6] Chapter 12 and 13 have illustrated how (in principle) we may determine, with simple neurophysiological means, for whom precisely will these approaches work, and on what neural systems and psychological functions are they effective. The "current ideas" are promissing, a body of knowledge is there, many details still need to be teased out, but the way forward has been indicated. I am grateful to each and all the authors for their contributions to this optimistic assessment.

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[6] One potentially fruitful line of inquiry concerns a new class of partial DA antagonists (M.Carlsson et al. 2004). A putative differential effect between cortical catecholaminergic synapses and extra-synaptic receptors is predicted from the proportionately high affinity of extra- *vs.* intra-synaptic binding sites, and thus the sensitivity of these sites should prove appropriate to low doses of the drug (A.Carlsson, 2004 personal communication).

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