Function and dysfunction of monoamine interactions in children and adolescents with AD/HD

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Introduction:

A consideration of how unusual function of the monoaminergic transmitters can contribute to the clinical picture of childhood attention-deficit/hyperactivity disorder (AD/HD) involves an understanding of 3 concepts: What are the main features of AD/HD, how does normal brain anatomy and function develop, and how do the monoaminergic pathways interact. With this context one is equipped to look at the evidence for unusual monoamine activity and interactions in contributing to the problems found in children with AD/HD.

This chapter proposes a way to integrate the features that these concepts have in common. The first part is concerned with a description of how childhood AD/HD appears in the clinic, at home or at school. This picture then acquires structure with specific features defined by laboratory testing. To understand what might be "dis-ordered" supposes knowledge of the organization in normal brain structure and in particular, how the organization of stimulus and response develops in the child and the adolescent. Important here is that much of the functional order is orchestrated by the monoamines. The third part sketches out where and how the long axon monoaminergic pathways reach out across brain structures and exert (normally) an adaptive modulation of function under changing circumstances. Further details are provided in other chapters.

I shall emphasize childhood AD/HD with modest reference to its manifestation in adults: I shall concentrate on the main three monoamines (dopamine, DA; noradrenaline, NA and serotonin, 5-HT) with but minor reference to adrenaline. Nonetheless this material has implications for the origin and course of AD/HD outside the early developmental period. Further, it will become apparent that the full consequences of changed monoamine activity can only be fully appraised within the context of the interactions with other amine- (e.g., acetylcholine) and amino-acid transmitters (e.g., GABA and Glutamate).

AD/HD – a clinical picture

The diagnosis of AD/HD usually concerns young people between the ages of 7 and 18 years. The manual of the American Psychiatric Association [APA: DSM-IV (1)] needs the presence of 6/9 features for the inattentive type, a separate 6/9 features for the type with hyperactivity and impulsivity, or both for the more usual combined type. The decision is based on longer structured or semi-structured interviews that ask 60-80 questions (or more) from two informants (usually a parent and a teacher) in order to show that the reported problems can occur independently of the situation. These features, impairing the function of the child, must have been present before the 7th birthday.

The health professional will get an image of motor restlessness (chair rotation, alternately sit or stand, move from toy to toy/task-to-task, fidgeting). Fine motor control can appear clumsy. Movement is often led by impulsivity. From observation alone it is often difficult to distinguish impulsiveness driven by a distracter, changing desires/motivations or an inability to withhold prepotent tendencies. Concentration is difficult unless the situation is novel. Social abilities are poorly developed (e.g., few friends, interruption of discourse), self-esteem is often low and the ability to organize or plan deficient. The latter can incur poor judgment and risk-taking. Changes in the quality of motivation-al features (e.g., the need to drink, assess reinforcement), stress- and emotional

control (e.g. temper tantrums) often complete the clinical picture [review (2)].

AD/HD – neuropsychological features

It must be emphasized that there is no function - typical of normal child development - that is completely absent in those with AD/HD. Lesions are not implicated. The patient is sometimes 'normal': but the problems persist in different contexts. A child appearing for an MR- or electrophysiological investigation can appear remarkably 'cool', for the time being. There have been innumerable disagreements over what constitutes a classical or 'core' phenotype. Of course, a way out is to define sub-groups by one or by another feature (e.g., referrals *vs.* non-referrals (3), inattentive *vs.* hyperactive-combined subtypes (4), with/without different comorbid disorders (5), internalisers [fearful anxious types]/ externalisers [fearless impulsive types, (6)], more or fewer than 7-repeats on the dopamine D4 receptor gene (7), those with high theta/low beta EEG ratios *vs.* those with high beta EEG power (8), medication responders/non-responders (9, 10) and more. It is ironic that the feature with the most widespread applicability appears to be that of intra-individual variability (11) – where it is the variance of response time that is usually considered.

Yet it is possible that the difficulties of AD/HD children can be both differentiated and reduced to a few conventional fields of ability. Thus, variance in the speed of performance relates to motor abilities in general, - in the sense of neuromuscular development (12), but also to poorly controlled supplemental motor activity and physiological state control (13). Similarly the variance in accuracy can be explained by inattentiveness (12), in the sense that distracters can delay (14), focused attention /non-target detection is slow (15), and indeed signal-detection indices of perceptual sensitivity (e.g., d-prime) are low (16, 17). The errors that so often result do not incur the usual slowing of the next response, - implying the impaired process-ing of feedback and contingent executive control (18, 19). There are two major processes here, - the top-down control of information processing, and the short-term sensitivity to reinforcement. If these are abnormal, one consequence is that children with AD/HD often express an aversion to delays in event-rates. In other words there are two separate features [dual pathway**,** (20)]: executive dysfunction and delay aversion make significant, independent contributions to predictions of AD/HD symptoms.

A number, if not all, of these features of AD/HD could be summarised under the rubric of a "disorder of impulsivity"(7). There is some truth in this. The term 'impulsivity' has 3 components, - acting on the spur of the moment (motor), not focusing on the task in hand (attentional), and not planning ahead [executive: (21)] that can all lead to ill-considered action. But it would be wise when attributing unusual neurochemistry to non-adaptive function to separate the control systems for cognitive and behavioural impulsivity (22). The alternative to lumping is to split the disorder into numerous sub-types. This will always have some explanatory value for specific features, but it is worth considering, for example, the experience of Nigg and colleagues (23). They examined executive function, motor abilities and flexibility of cognitive set, and found that the similarities between diagnostically inattentive and combined subgroups were much more striking than the differences [cf. also (24)].

Unusual brain functions in children with

AD/HD are associated with inattention (perception and selection), poor controlled-(executive)-decision processing (conflict management), non-adaptive evaluation of reinforcement contingencies and situation-ally inappropriate motor activity. These impairments are reflected in each of the successive stages of information processing that are so clearly and precisely represented by scalp electrophysiological records (event-related potentials, ERPs) in the first half second after an event: Stimulus-elicited cortical excitation [N1 reduced, (25)], interference control [P2 larger, (26)], stimulus categorization [N2 reduced, (27)], effortful updating of short-term memories (P3 reduced, (28)], assessment of stimulus 'targetness' [processing negativity reduced, (29)], assessment of mistakes [error-related negativity/Ne/Pe reduced, (30)], and motor organization (LRP reduced, (31)].

Normal brain development

With an interest in AD/HD in mind, interest in normal anatomical and cognitive development centres on the classical peri-pubertal age for referral (8-14y) with curiosity extending to earlier features (potentially relating to causality) or how matters progress or disappear in young adults.

Myelination, white matter development, begins in the second trimester, develops linearly from 4 years & continues through (and beyond) the third decade. In the meanwhile frontal lobe gray-matter develops slowly and gradually to 8 years of age when prefrontal development (rostral to the precentral sulcus) takes off and develops rapidly until about 14y. Having peaked prior to adolescence, the grey matter volume then declines (32). This process is attributed to the pruning of connections (33), and may start as early as 7 to 10 years of age in sensory and in frontal association cortices, respectively. The thickness of the cortex decreases across the whole period from 8-20y (34). The peripubertal age also sees the rise of hemispheric differences (e.g. around the inferior frontal sulcus: cf. language development on the left). Some of these differences are gender specific (35).

Brain, especially white-matter-volumes, increase continually over 3 decades: overall increases of volume are found in many parts of the frontal, parietal and mid temporal (limbic) lobes, while more definite decreases occur in the lateral cortices, basal ganglia and thalamic nuclei (36-38). These studies have shown that maturation progresses in waves, rostrally in the frontal and laterally in the temporal lobes. Interestingly these separate developmental axes are reflected in a functional study showing the 'migration' along these axes of the sources of activity underlying the detection, registration and response to changes of auditory stimulation (39). Such maturational processes continue into the frontal and temporal poles throughout the third decade. Indeed, frontal grey/white matter ratios continue to decrease (linearly) even beyond that age (40).

Normal neuropsychological development

Linear increases in the rate of development of postural and sensorimotor coordination peak around 6 and 10 years of age, respectively. Continued development, particularly of the latter, depends increasingly on experience and its consequences, - described as 'enhanced programming resources' and online feedback processing (41, 42). Tapping in to such problems may reflect the core problems of AD/HD children in cognition, on which this chapter concentrates. Thus, it should be borne in mind that motor coordination does not become mature until

relatively late (in the second decade), alongside attentional and executive functions (38). In contrast sensory functions, orientation and speech-related abilities develop earlier in the first decade.

In late childhood (around 7y ± 1y) children make a qualitative leap in their cognitive abilities, allowing measures to be made of tests that have a qualitative if not a quantitative similarity to those used in the neuropsychological testing of adolescents and adults. In particular they are able to orient between cues and master conflicting stimuli about as well as older children (43). However the speed and accuracy of switching attention continues to improve with age.

As would be expected from anatomical developments briefly described above, the transition of puberty (around 12 ± 1y) coincides with the maturation of many abilities associated with the function of the frontal, or especially the prefrontal lobes. These include abstract reasoning, use of goals in making plans, inhibitory control, verbal fluency, verbal delayed recall, novelty-seeking, even finding a degree of independence from the family (35, 44).

But fine grain analyses of development have been rare. A series of studies by Luna and colleagues (45) on speeds of processing, the ability to inhibit voluntary responses and working memory use were all based on variations of an oculomotor task, thereby controlling for the comparison of qualitatively different task requirements. They reported that adult levels of response inhibition were not achieved before the age of 14y[1], independent of speeds of processing that matured a year later. Working memory performance, which depended modestly on the other two variables considered, did not attain adult levels until 19 years of age.

The development of the stages of information processing is illustrated in an exemplary way with ERP measures. The arrival of sensory information in the thalamus and sensory cortices is marked by the P1/P50. Maturation to adult levels involves a decrease of amplitude and latency by about a third between 5 and 15 years (48). The gating of the ERP response to a second stimulus (as marked by P50 in a paired click paradigm) is extremely variable at puberty (49), and may not achieve adult expression until the end of the teens (50). The development of excitation elicited by a salient stimulus (N1), along with the suppression of processing of other stimuli (P2) - as a preliminary to its being further processed – has been described for subjects aged from 5 to 30 y (51, 52). The N1/P2 adult waveform only becomes evident at 13-14y of age. The decreases of the latency and amplitude characteristics of the peak and the dipoles do not mature until after 16 years. Around puberty the topographic distribution of the P50 peaks across the scalp move posterior and N1 peaks lose their rightward asymmetry However, P2 peaks do not move rostrally to their central adult locations until the end of adolescence. The categorization of stimuli (marked by N2) and context-updating (marked by P3) attain their bilateral frontal and parietal topography by around 17 years of age. The amplitudes of these components show a linear and curvilinear development with age, respectively, and mature around 15 years of age with latency attaining adult

[1] The emphasis is on adult levels of performance. In the preceding peri-pubertal phase children can execute such tasks (e.g. Go/no-go) but they recruit much larger areas in the frontal lobes (46) and the amplitudes of the ERPs show that their categorization of stimuli and evaluation of errors made on these and conflict tasks are in general remarkably small (47).

levels some 3 years later (53, 54). Indicators of automatic selective processes (Mismatch negativity, MMN) develop about 3 years earlier than controlled attention-related processes (Negative-difference, Nd). While MMN topography becomes bilaterally distributed after puberty, the latency reaches adult levels around 17 years, but the dipoles continue to migrate along with normal frontal and temporal lobe expansion through the third decade (39, 51).

The monoamine pathways

As their names suggest there are three major dopaminergic (DA) innervation systems in the forebrain, with their mesencephalic origins in the ventral tegmental area (VTA) and substantia nigra (SN) in the brainstem – the mesocortical, mesolimbic and nigro-striatal projections (55). The density of mesocortical DA pathways in primates increases rostrally across the cortices. For example, the increase in the rostral auditory association cortices is already markedly higher than in the more caudal temporal lobe. A moderate then higher innervation is found moving from somatosensory over motor to prefrontal association areas. The axons are especially dense in layers I and II and again in V and VI (56). DA D1 receptors (dense in I-IIIa, moderate in V and VI) are present at one to two orders of magnitude more than those of the D2-family; but in this D2-family the D4 type of receptors are more evident in the neocortices (e.g. layer V), and the D2 types in the limbic and temporal regions. Important recipients of mesolimbic innervation include the entorhinal and cingulate cortices (transitional and archicortices), parts of the hippocampus and amygdala, and the ventral striatum (nucleus accumbens and septum). Oades and Halliday (55) pointed out that these regions are 'nodes of convergence' of input from very many brain regions and represent excellent opportunities for DA activity to influence the shifting of the control of their efferent output between different afferent sources (figure 1).

The main noradrenergic (NA) projections to the limbic and cortical brain regions of concern here arise in the locus coeruleus (LC) of the pontine brainstem. NA fibres project throughout the forebrain, to the phylogenetically older archicortices (hippocampus and amygdala), the neocortical mantle, but also the cerebellum. This more dorsal pathway along with a more ventral one from the nucleus tractus solitarius also innervate several subcortical regions including the thalamus and hypothalamus (57). Innervation in the neocortices increases from layers I-V with highest densities in II and IV with greater densities of the alpha and beta receptors in the more superficial layers (56). Alpha-2a sites, prominent in frontal regions, may be pre- or post-synaptic in location, while alpha-1 sites more often exert effects pre-synaptically: the former inhibiting, and the latter enhancing monoamine release (58).

Relevant to forebrain function, 5-HT projections originate in the median and dorsal raphe on the border of the pons (containing the LC) and midbrain (containing the VTA). There is some overlap between the areas innervated, but the dorsal raphe projects more anteriorly, to the frontal cortices and basal ganglia, and the median raphe somewhat more to limbic structures and the diencephalon. The sensory and motor cortices display a decidedly patchy distribution of low and high levels of innervation (59). Much of the input arrives in layers III and IV (60). Two of the most studied 5-HT binding sites in the CNS are the

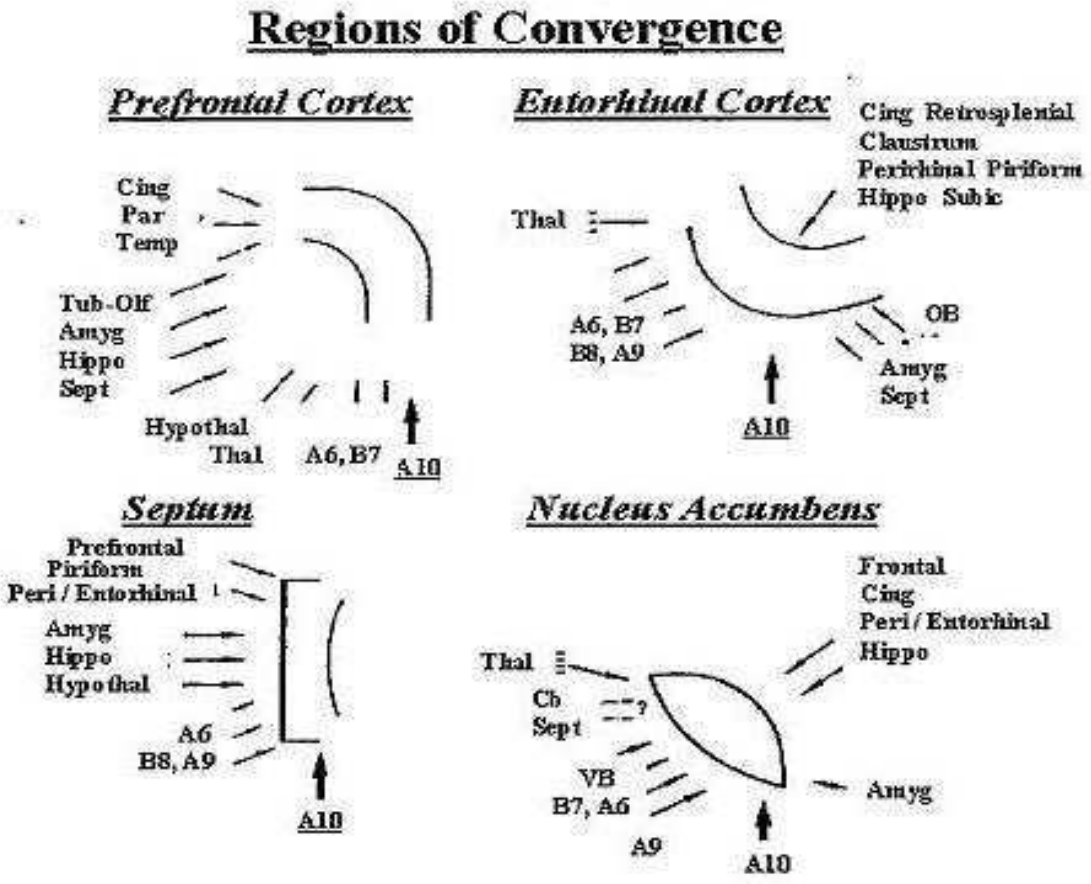

Figure 1

Nodes for the convergence of afferent fibre input on two mesocortical and two mesolimbic DA projection regions (prefrontal and entorhinal cortices, the nucleus accumbens and septum). Reproduced from (55) with permission from Elsevier.

Amygdala (Amyg), Cerebellum (Cb), Cingulate cortex (Cing), Claustrum, Entorhinal cortex, Frontal cortex, Hippocampus (Hippo), Hypothalamus (Hypothal), Infero-temporal cortex (Temp), Olfactory bulbs (OB), Parietal cortex (Par), Prefrontal Perirhinal, Piriform and Retrosplenial cortex, Septum (Sept), Thalamic nuclei (Thal), Tuberculum-olfactorium (Tub-Olf), Ventral noradrenergic bundle (VB): Monoaminergic nuclei (A/B 6-10).

5-HT1a and 5-HT2a receptors. The former is often characterised as an autoreceptor, and the latter postsynaptic, but this is not an exclusive compartmentalization (e.g. 5-HT1a sites are active postsynaptically on cholinergic neurons). Stimulation of either site can lead to increased catecholamine outflow[2] (61-64).

Monoamines - development

DA neurons enter the cortical plate early in the second trimester. DA has a trophic role at this early stage, whereby impairments can have consequences on the later thickness and connectivity of the cortex (65). From birth to puberty the

[2] This generalization glosses over the variation with brain region, receptor sub-type (e.g. 5-HT2c, 5-HT1b), the mechanism (through an effect on release or synthesis) and whether the catecholamine neuron is in a tonic- or burst-firing state.

number of axons can increase 6-fold before pruning processes set in. Numbers of DA receptors peak in mid-childhood, already decreasing well before puberty [D1 earlier than D2: (66, 56)]. Across adolescence to adulthood the number of D1 sites falls by nearly 50% and D2 sites by nearly 60% (67): thereafter numbers of D1 sites decrease by a few percent per year. The implication that the D1/D2 ratio falls with age is notable. In studies of rodents the peak for D2 receptors seems to be larger in males, and despite the ensuing reductions, levels are still higher than in females through adolescence (68). (The same study also described more D1 sites in right than left sided subcortical regions that lasted from the post-pubertal period into adulthood: this is reflected by measures of DA and its metabolite DOPAC that showed a lower turnover in the left hemisphere until inter-hemispheric coupling matured in young adulthood (69). Such findings are yet to be confirmed for humans.) The DA transporter system follows a different course, peaking at puberty and gradually decreasing right on through to 50 or 60y of age [postmortem study: (66)]. This matches the inverse changes for the synthesis of DA (by tyrosine hydroxylase) that in non-human primates continues to develop right through into adulthood (70). The gradual decrease of transport mechanisms may accurately reflect functional activity, and are directly reflected by the gradual decrease of DA turnover seen in urinary measures taken between 10 and 20 years of age (71).

NA development in the human foetus follows but at first lags a little behind that for DA in the perinatal period (72, 73); but if data from animal studies pertain then it soon speeds up and overtakes that for DA (74). In studies of primates and other animals alpha-2 and alpha-1 types of receptor also follow each other in developmental waves, with the alpha-2 ahead at birth. But levels fall off after birth as numbers of alpha 1 sites increase. Yet by puberty alpha-1 sites are decreasing more rapidly than the alpha-2 sites. Transport mechanisms are gradually reduced following puberty but increase again by the end of adolescence [review (59)]. This post-pubertal decrease followed by an increase across the teenage period is reflected in urinary indicators of NA turnover (71).

5-HT development reflects first a prenatal neurotrophic role, and second a postnatal expansion of neural innervation and function. A study of Rhesus monkeys from 2 weeks to 10 years of age (70) showed that while the development of catecholamine-containing appositions on cortical pyramidal cells reached half adult levels by 6 months of age – 5-HT appositions had already attained adult levels by 2 weeks. Prepubertal development, though considerable, appears paradoxically to be functionally slower than that for DA, such that CSF measures suggest a near doubling of the ratio of DA to 5-HT metabolites over the prepubertal period [review: (59)]. Post-mortem tissue (75) and urinary measures (71) suggest that rather like the situation with NA, 5-HT turnover decreases initially post-pubertally, but then rises again at the end of the second decade. If studies of rodent development are any guide considerable lateralised differences are to be expected. Neddens and colleagues (76) reported a rightward emphasis of fibre density in the neocortices and a leftward emphasis in the limbic cortices.

Clearly there remains alot of detail on the development of the various features of monoamine systems to be described: the near absence of knowledge of the relative abundance of the different receptor

subtypes is striking and only partly explained by the fairly recent availability of suitable ligands. The results reported in this section show that there is no simple way to say that the functional activity of one or the other monoamine (let alone their interactions) is more or less than adult levels at a given age. First the baseline of adult levels is continually changing with age. Secondly it remains unfortunately equivocal whether any specific function considered is more accurately represented by turnover, synthesis rates, transport mechanisms or the development of synaptic appositions on innervated pyramidal or non-pyramidal cells. Each of these features develops at different non-linear rates.

Monoamines interactions pertaining to normal cognition

Brain-damage or insults to the monoamine systems alone do not allow unequivocal conclusions to be drawn about hypo- or hyper-function in the affected system. But they do provide some insight into the normal situation by seeing in what domains there are dysfunctions. Preclinical studies [e.g. reviews: (77-79)] suggest that damage impairing NA function increases distractibility. NA tunes the influences of the inputs competing to control the output of an NA innervated region. Low to high tonic firing rates are associated with inattention and low arousal to agitation and stressed states. In contrast phasic firing occurs when stimulation is relevant, other activity should be tuned down (80). Impaired 5-HT function is associated with impulsivity, whereby decreased function may relate to outbursts of aggression, while increases are associated with cognitive impulsiveness (81-83, 22). By analogy with the role of NA in tuning, studies of stimulus control suggest that 5-HT very often appears to influence transmission by exerting a volume-control or gain function (59;84). By contrast, the role of (increasing) DA activity has been described as one of facilitating the likelihood of a switch occurring between one of two inputs controlling the output of a given brain region (79). Reducing DA function thus leads to the slowed switching in of a particular cued response (85). This can be advantageous in initial learning. In contrast, high activity enhances switching as in divided attention, or between attentional and task sets [e.g. trail making, or discrimination reversal: (86, 87)]. While low and high levels of DA and NA activity, respectively demonstrate the different roles of tuning and switching in initial learning there are other situations in the control of ongoing behaviour when their function can appear rather similar as a result of the presence of different receptor subtypes[3].

There are numerous complications that make for difficulties in the interpretation of the results of the manipulation of any one of the monoamines. I shall mention a few. NA neurons have sites that will transport NA and DA, and others that can release NA or DA (89). This makes it very difficult to determine precisely the mechanism by which, say, psychostimulants achieve a specific cognitive effect. Questions are not limited to the role of DA. NA is known not only for its high affinity for the alpha-2 and low affinity for the alpha-1 binding site, but is a relatively good ligand at the DA D4 site (90). Interactions between the two

[3] Arnsten (77) provides an example of NA involvement in switching between channels of activity. Information may be faithfully transmitted from the thalamus to the cortex under conditions of sufficient NA release to engage $\alpha 1$ and β NA receptors. But when low levels of NA are released $\alpha 2$ receptors are engaged. Then, thalamic neurons enter a burst mode which prevents information transfer (88). In this way, the varying affinities of NA for $\alpha 2$ vs. $\alpha 1$ or β NA receptors acts as rather like a 'switch to alter neuronal, and the ensuing behavioural state.

catecholamines are also documented. For example, NA receptors have even been hypothesised to 'gate' DA release (91).

It has long been realised that 5-HT input frequently inhibits DA activity: now a better understanding of the HT2a binding site has shown that this effect must also extend to the NA system (64). However, opposite effects on catecholamine release are attributed to HT1b, HT1d and HT3 binding sites. The fact that both alpha-NA and 5-HT1 sites may be found in pre- and post-synaptic locations warns against generalizing about a transmitter's activity being associated with one-dimensional changes of any one cognitive ability (59).

AD/HD: (1) Indicators of Monoamine Metabolism - theory

Let us take a 'top-down' approach from the viewpoint of theories currently advanced to explain AD/HD problems. There are 2-3 broad explanations that nonetheless do not account for all features and 2-3 that account for a domain of dysfunction, but extension beyond these domains remains controversial.

First there is the dual pathway theory (92) and the cognitive energetic model (93). The former directly invokes monoaminergic involvement and provides the background to the rest of this chapter. The latter is pitched at the psychological level of state regulation with physiological underpinnings, but elaborates little on the monoaminergic contribution. A related account (13) explicitly accounts for a range of AD/HD problems (variability and maturation) at the level of energy availability in CNS function, but only indirectly invokes modulation by the monoamines.

Other theories aim at generalizing from specific domains of performance such as response inhibition (94, 95)to executive function and affect control, and the 'dynamic developmental theory' (96) that concentrates on the registration of reinforcement and related motivational consequences [see also reviews in (5, 97)]. All these theories depend on functions modulated by DA (prima unter pares). They tend to overlook the role of NA and 5-HT, but do admit dependence on the interactions with excitatory and inhibitory transmitters (Glutamate, GABA and acetylcholine), without much elaboration.

Most of these theories also do not pay adequate attention to explanations that could account for rates of comorbidity, maturation lag, impulsivity, stress-responsivity and sleep-wake patterns, to name a few other abnormal features associated with the phenomenon of AD/HD.

AD/HD: (2) Indicators of Monoamine Metabolism – a dual pathway

This theory invokes a role for the mesocortical DA system in modulating (deficient) dorsal fronto-striatal glutamat-ergic mediation of some executive functions. It also envisages a role for the mesolimbic DA system in the anomalously functioning reward and motivation-influencing circuits of the more ventral frontal-accumbens glutamatergic system (92).

Mesocortical pathway

Direct evidence for the involvement of the mesocortical pathway is rather recent. Neuroimaging evidence from subjects with AD/HD suggests less activity in the right prefrontal regions and parts of the basal ganglia (the caudate nucleus and pallidum) during a continuous performance test of sustained attention [in children, (98)], but also in these areas (inferior frontal) and in the cingulate region during stop-signal and Go/no-go tests of impaired response

inhibition and impulsivity (in adolescents, (99-101)]. Indeed, no significant increase was found in AD/HD children on interference suppression [as exhibited during performance of a flanker task: (102)], where the activity recorded in normal children in the mid- and inferior frontal regions correlates with success (103). The emphasis on right inferior frontal regions is warranted by a detailed study relating the location of brain damage to stop-task performance in brain-damaged adult subjects (104). But we should also note with regard to the fMRI studies that blood oxygenation (BOLD) signals are low across many brain regions, - even in the cingulate gyrus during Stroop tasks when performance in the interference condition was actually unimpaired (105).

In general MR-anatomical studies of AD/HD subjects give little clue as to whether any particular region, such as those just mentioned, is altered in size or development. A small reduction is recorded as widespread through the cerebral and cerebellar lobes (106). However, grey matter reduction in the right prefrontal (107) as well as in the caudate regions (108) in these studies is noteworthy.

The prefrontal and cingulate regions discussed receive a mesocortical DA innervation. But is DA involved? Relevant to this point are further studies on the ability to switch attentional set. The ability as tested by the trail-making test has been identified as potentially belonging to the core cognitive endophenotype of AD/HD (23). In a task where the subject had to map words/symbols to response hand under changing conditions, switching proved especially inefficient for those with brain damage to mid- and the already described right inferior frontal region (109). Such switches have been related to DA activity (79), and in accord with expectations methylphenidate enhances performance of AD/HD children in the stop-task (110) and reduces the cost of switching between letter/number sets (111, 112).

As one of the striking features of prefrontal blood flow activation during cognitive challenge is that these are absent or reduced in adolescent and adult subjects with AD/HD [fMRI above, also PET studies, (113, 114)], it is important to note that behavioural responses and brain activity in these regions are altered by methyl-phenidate treatment. However, while thalamic or cerebellar activity may increase, that in the relevant frontal regions *decreases* (115). This must in part be a reflection of the marked increase of synaptic DA (and blockade of DA reuptake [50% at therapeutic doses]) known to follow treatment with methylphenidate in healthy subjects (116). In turn such changes have been directly and quantitatively linked to the interest, motivation and success in subjects who completed simple maths tests (117). However, two further findings provide a clue of how, with care, these results should be interpreted. Firstly, in cocaine-addicts methylphenidate actually increases metabolism in BA11 and BA 25 (orbitofrontal cortex) regions registering salience, motivational and emotional reactivity (118). Secondly increases of PET metabolic measures were recorded after double dosing (119). In both situations increases of DA D2 binding are expected, and it is binding in the DA D2 family of receptors that correlates with metabolism across a whole range of frontal cortical regions (120). Indeed, the variability of biochemical or behavioural response depends on the individual baseline for DA D2-like binding.

So one may entertain the hypothesis that

the AD/HD deficit may be related to an unexpected low or a relatively low level of DA binding in the individual, and his or her baseline binding status. However, if an increased chance of binding is to be therapeutic, it should probably reflect the rapid on/off (high k_{off}) type (i.e. impulse related). The reasoning is first that synthetic activity marked by PET studies of DOPA decarboxylase are lower in frontal regions of adult AD/HD patients (121). [Higher levels seen in the midbrain of younger patients (122) may reflect the mesolimbic pathway (see below).] This would lead to a low availability of DA especially when there is impulse activity. Secondly, a faster clearance of DA (by catechol-o-methyl transferase, COMT) is associated with improved performance in tests of sustained attention and time estimation (123, 124) - especially in the inattentive type of AD/HD patient. Faster clearance is achieved by those with the valine variant of a functional polymorphism (Val158Met) of the COMT gene than by those with the methionine variant.

Now we should add the complication that in the frontal cortices the binding site referred to may be the DA D4 site that is the more abundant member of the D2-family present. The type of rapid binding referred to above may well be influenced by the number of transmembrane repeated elements to be found in the molecular structure of the receptor. The D4 gene with 7 (or 2) repeats may be the form showing biased transmission in Occidental and Asian samples of AD/HD (125, 126). Currently the contrast of groups with or without the 7 repeats shows relevant but rather minor cognitive problems. Those without the 7 repeats showed more variable responses, longer response times and were mildly inattentive (7, 127). Those with 7 repeats were without problems on a colour-word, cued detection or rapid choice reaction time task (127), yet more impulsive on a Go/no-go task (7). A third laboratory has reported that homozygotes for the 4 repeat form tended to be those with a reduced brain volume (128, 129). Our understanding of the mechanisms at work here is clearly in a process of evolution, but the evidence points to important variability in DA D4 function in AD/HD.

Cortical NA

With the, as yet, modest effects noted to be associated with several (but not all) forms of the D4 binding site, one should consider the interaction of the mesocortical DA system with other monoamines. The intimate interactions of NA with DA processes cannot be overlooked. The NA transporter (NET) can take up both NA and DA (130). Such neurones can also release both NA and DA (89, 131). Further NA is a high affinity ligand for the DA D4 binding site (78, 90). NA receptors may even control the cortical release of DA, - for with the alpha-1b site knocked out animals showed no extracellular release of DA in response to amphetamine treatment (91). The role of NA must be considered in view of the well documented therapeutic effects of the newer (atomoxetine), as well as the older uptake inhibitors (desipramine, imipr-amine), the alpha-2 agonists (clonidine, guanfacine), let alone the psychostimulants methylphenidate and amphetamine that affect both catecholamines similarly (132).

The role of NET in the function of the “mesocortical pathway” is prominent in the response to methylphenidate, as it is far more abundant than the DA transporter (133). Indeed some changes in the NET genotype (G1287A, NET1) have already been reported to be associated with AD/HD (134) and in particular the symptoms of

hyperactivity and impulsivity (135): [pace negative results for *other* polymorphisms in three studies (136-138)]. These symptoms are improved by atomoxetine treatment (139). Tantalising but as yet equivocal evidence has been reported for associations of polymorphisms of the synthetic enzyme and alpha-2 receptor sites with inattentive symptoms (140-142).

Effects of NA associated with cognition probably occur through one of the 3 forms of the alpha-2 receptor located largely postsynaptically and with a high affinity for NA. [Alpha-1 and beta sites have a lower affinity for NA and may come in to action in stress situations associated with high levels of NA (77)]. In the monkey model infusion of guanfacine into the ventrolateral PRF strengthened associative learning and impulse control (143, 144). In dorso-lateral regions an alpha-2 antagonist induced some behavioural hyperactivity, more errors of commission on sustained attention tasks and no-go errors on Go/no-go tasks (77, 145, 146), reminiscent of the features of AD/HD children. These effects are consistent with what we know about the normal role of NA. The locus coeruleus, the pontine nucleus of origin of the cortical NA fibres, shows tonic slow firing rates in the waking state: the appearance of stimuli relevant to the ongoing situation elicits clear phasic increases of neuronal firing, thereby also suppressing responses to irrelevant stimuli (80). This role is consistent with a 'tuning' function for NA activity (79).

While published descriptions of neuro-imaging studies relevant to the role of NA in AD/HD are still awaited, there are some data from electrophysiological studies. The sort of AD/HD subject that profits from imipramine treatment (that may affect NA and 5-HT systems) is one who shows EEG characteristics of a maturational lag (147): these subjects show a widespread increase of theta power – expected to decrease with development - but reduced power in the beta and alpha bands posteriorly). The theta power also tends to normalise following methylphenidate treatment, especially over right frontal regions (148). Robust clinical responders to psychostimulant medication show an anterior/posterior ratio of the P300 ERP amplitude exceeding 0.5: just over half of the subjects tested on atomoxetine also showed this characteristic (149). In a visual or auditory oddball paradigm methylphen-idate treatment is associated with increase-ing the small P3a and P3b characteristic of unmedicated patients (148, 150, 151). Indeed sometimes both latency and the amplitude variability across subjects is reduced by methylphenidate treatment (152). The enhancing effect on P3 (and processing negativity) is largely seen with target processing, consistent with an NA facilitated tuning effect (153, 154). Probably reflecting both the NA and DA effects of methylphenidate, stimulant treatment also normalises early stages of information processing (a reduction of the large N1 and P2 amplitude, and increases of the size of the N2 in Go/no-go tasks: (155, 156).

Cortical 5-HT

It is not widely appreciated that changes in the 5-HT system may contribute to the clinical picture in AD/HD. This view arises out of the lack of an effect of the major pharmacotherapeutic agents on 5-HT activity[4]. Hence there have been few studies of direct relevance to this chapter. Genetic,

[4] It is also not widely appreciated that atomoxetine binds to the 5-HT transporter with an affinity, very approximately, only an order of magnitude less than for the NET. For comparison it binds to DAT with an affinity three orders of magnitude less, and methylphenidate has an affinity for the 5-HT transporter well over 4 orders of magnitude less (157).

biochemical and neuropsychological evidence has recently been reviewed (59).

One must first bear in mind that in brain regions where there is a common innervation from DA and 5-HT fibres, 5-HT activity modulates that of DA. Receptors are found on mesocortical DA fibres where HT2c sites modulate tonic DA outflow, while HT2a sites affect active DA transmission (61, 158)[5]. Thus it is not surprising that CSF measures of the metabolites of both monoamines are often inter-correlated, and were reported to decrease in AD/HD subjects responding to methylphenidate treatment (162).

From a functional point of view shifts of attention facilitated by methylphenidate are impaired by reducing 5-HT synthesis in healthy young adult subjects (163). Let us take the example of the cognitive challenge of conditioned blocking. Healthy children switch out the influence of superfluously related stimuli while learning a conditioned association (164). This is associated positively with levels of DA metabolites (HVA) excreted, but negatively in AD/HD children experiencing difficulties with conditioned blocking. Additionally the AD/HD children showed a positive association with the removal of 5-HT metabolites (5-HIAA). This is consistent with the AD/HD children removing high levels of 5-HIAA and showing low HVA/5-HIAA ratios of relative metabolic activity. This result contributed to the authors' suggestion that with respect to 5-HT activity AD/HD children show hypodopaminergic activity (165). This is also consistent with the authors' report of correlations between cognitive impulsivity measured on the stop-task and decreasing affinity of the 5-HT transporter, that would lead to higher levels of 5-HT in the synapse and correspondingly more metabolism (22). Rubia and colleagues (166) also report fMRI evidence from young adults of cognitive control by the 5-HT system. Decreased 5-HT synthesis induced by an amino acid drink related to more left-right hand choice errors on a Go/no-go task using arrow-cues. The change in 5-HT levels was associated with decreased BOLD signal from the inferior and orbital frontal cortices, but an increased signal in the temporal lobe. (The former regions were noted above to be of special interest in explaining function in AD/HD.)

In continuous performance tests, perceptual sensitivity (d-prime) falls with an increased excretion of 5-HT metabolites (16). The relationship of DA to 5-HT activity (HVA/5-HIAA) is depressed in some samples of AD/HD children (165), although increases of this ratio may reflect motor activity (167). Let us consider some direct measures of the role of 5-HT in the processing of salient stimuli in the sensory and association cortices.

The amplitude of the N1 to P2 ERP elicited by auditory stimuli can depend on their loudness. These two components reflect the excitatory response to salient stimuli and the allocation of resources for further processing. The augmenting response reflects 5-HT neurotransmission and has been used to predict clinical responses to 5-HT agonists in affect disorders (168). The slope is decreased following 5-HT uptake inhibition (169). Although the activity of other transmitters (e.g. DA and acetylcholine) can also influence responsiveness (169, 170), the P2 component can be viewed as a marker of the role of 5-HT in the interplay with the catecholamines in the auditory cortices (171). Long ago it was noticed that the response of autistic children to fenfluramine

[5] The HT2a effects are better documented from the mesocortical projection, and the HT2c effect on tonic DA outflow from mesolimbic projections (159-161)

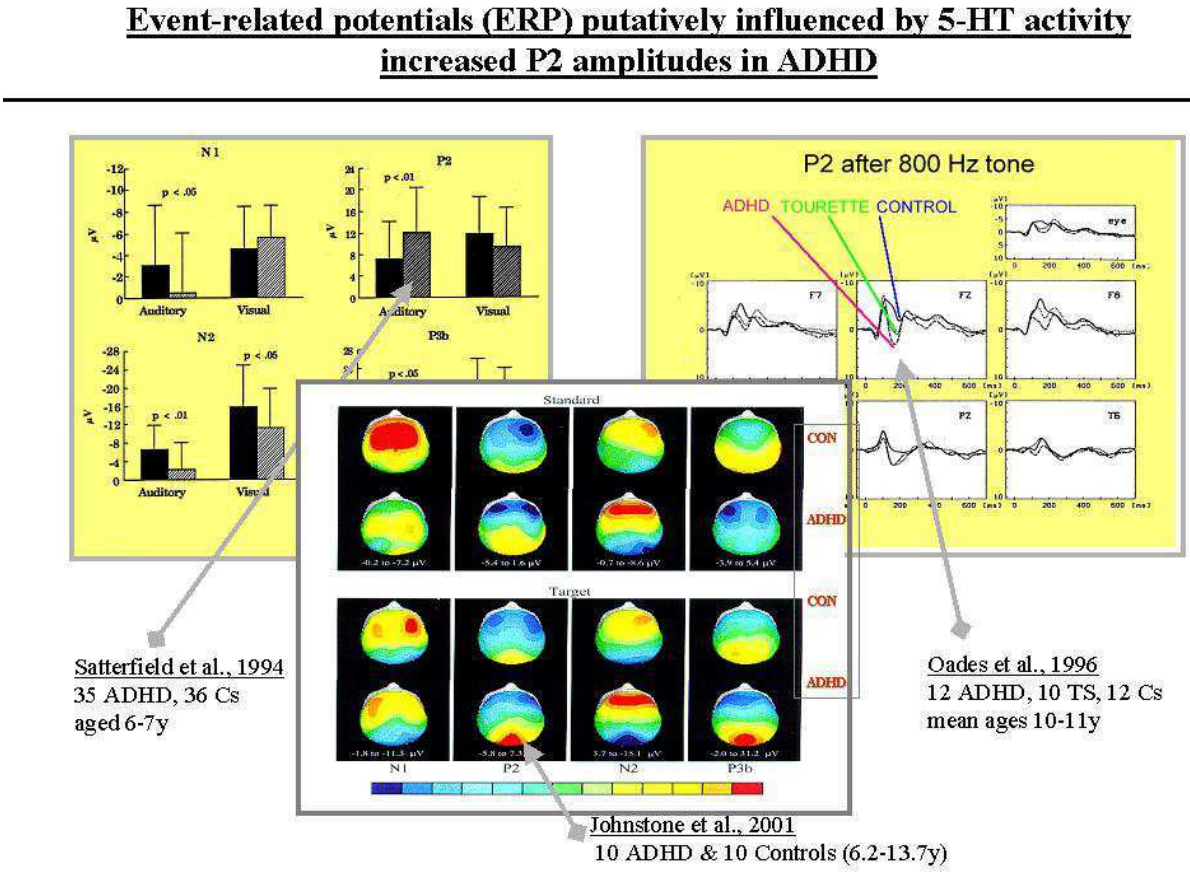

Figure 2

Three ERP studies of AD/HD children showing a P2 component of large amplitude that may reflect anomalous serotonergic activity. [The figures are modified after (26, 249, 250) and reproduced with the permission of Elsevier, Blackwells and the author, respectively.]

and AD/HD children to methylphenidate could be predicted by the augmenting response (172, 173). More recently, numerous studies describe the frequent occurrence of unusually large P2 amplitudes in AD/HD children – three are illustrated in figure 2. The 5-HT influence may be more widespread. 5-HT suppression through amino acid drinks increases mismatch negativity (that marks the detection of deviant stimulation) – so increased activity may impair. The impairment of right frontal MMN in AD/HD children may reflect this (26). The MMN sources known to include the right inferior frontal region are also those noted in fMRI studies (discussed above) to be sensitive to AD/HD impulsivity and 5-HT activity (99, 166). One of the other sources of mismatch negativity is located in the cingulate cortex (174), alongside dipoles for the event-related responses recorded after error commission. One of these components (the Pe) may be reduced in AD/HD children (19). Responses to error commission are sensitive to the activity of the 5-HT transporter. Variations in the transcriptional control region of the gene (5HTTLPR) come in short and long versions. The low activity short variant is associated with larger error responses in healthy subjects (175) – so that one would predict that the long variant may be associated with

reduced Pe. Indeed biased transmission of the long allele has been reported recently for AD/HD (176). Associations of the one or the other form with the 7-repeat DA D4 allele have been related to opposite extremes of temperament and anxiety in infants (177), and together with those for 5-HT may represent significant markers for AD/HD (178). Lastly, supporting the thesis of over-activity in the 5-HT system, reductions of the 5-HT metabolite have been noted for hyperactive children responding to medication (179).

Against this background, it may be borne in mind that there are several mechanisms that could mediate the 5-HT/DA interactions in AD/HD. Thus, the nature of the 5-HT transporter (5-HTTLPR) will affect the expression of 5-HT binding sites: for example the short allele is associated with a lower binding potential of the HT1a site (180). Agonism here is associated with reducing 5-HT activity that inhibits DA release in terminal regions (181). This could be one mechanism to combat hyper-serotonemia. In contrast, agonism at DA D2 sites has been shown in microdialysis investigations directed at the dorsal raphe origin of 5-HT projections to increase 5-HT release (182, 183). This would suggest caution in the exploration of useful DA agonists. With regard to ongoing treatment with methylphenidate, 5-HT agonism (quipazine) in animals can interact to enhance the down regulation of the DA transporter (184). On the presynaptic bouton stimulation of both the D2 autoreceptor and the DA uptake site can change the sequestering by the vesicular monoamine transporter (VMAT-2) of transmitter be it DA or 5-HT (185, 186)(figure 3).

Mesolimbic Pathway (DA)

Leading animal models agree that the DA transporter (DAT) appears both to work inefficiently and be over-expressed in the mesocortical pathway. By contrast, these models disagree on the nature of the different situation in the mesolimbic system (187). Mesocortical function is dominated by the NET control of both DA and NA clearance and release, exacerbated by disorder in the relatively sparsely distributed DAT control. NET is barely present in most of the regions modulated by the mesolimbic projections, but DAT is prominently represented.

The major targets of the mesolimbic DA pathway ascending from the mesencephalic VTA are the nucleus accumbens, amygdala and the hippocampal complex (55). These regions receive topographically distributed glutamatergic input from dorsal and orbital frontal cortices, and provide feedback via GABAergic and glutamatergic pathways over several thalamic nuclei. Unusual activity in these constituent circuits modulated by the mesolimbic afferents are postulated to account for the aversion of many AD/HD children to delays. They can wait, but usually prefer a small reinforcement over waiting for a larger one [reward discounting: (92)]. Support for this being a prominent determinant of AD/HD behaviour comes from many studies (188-191). This characteristic is interpreted as an inefficient coupling between current responses and future rewards. The result is a reduced control by future salient events on current events – the gradient between the two is short and steep (96).

The difficulty lies not in arguing whether there are problems in processing delays and discounting rewards in children with AD/HD, but in refining our understanding what are the components of this phenomenon. For example, animals with lesions of the amygdala also prefer immediate over later,

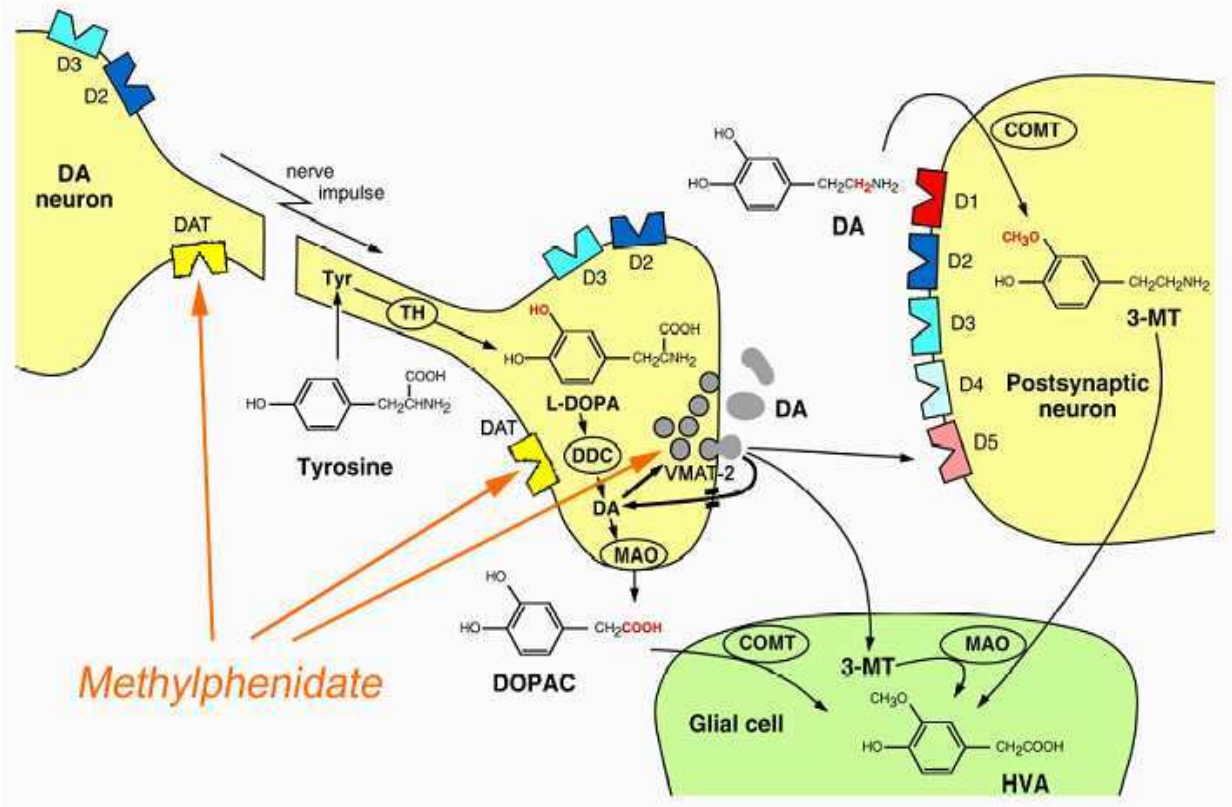

Figure 3

A scheme illustrating the synapse of a dopaminergic neuron, with the presynaptic bouton on the left at the end of an axon leading from the cell body, and the post-synaptic element on the right. The 5 types of DA receptor that may occur post-synaptically are illustrated although they would not all be found in the same synapse. The contribution from an astrocyte is symbolised by the glial cell below. The synthetic pathway for DA is illustrated pre-synaptically. The points for the potential action of medication (methylphenidate) are illustrated as a) the DA transporter on the cell body and on the bouton, and b) the vesicle monoamine transporter (VMAT-2) where newly synthesised DA is taken up prior to exocytosis in the cleft: [modified after (96) and reproduced with the permission of Cambridge University Press]

larger rewards. However damage to the input from the orbital frontal cortex has the reverse effect (192). This could be described as a system that controls 'impulsivity' (193). Do meso-accumbens DA pathways mediate incentive motivation and reward (194) or do they (more parsimoniously) enhance a switch between circuits influencing the processing of more or less salient information (195) It should not be overlooked that communication about reward (via some DA pathways) has much to do with its mediation by the orexin / hypocretin output from the lateral hypothalamus and amygdala (196).

At the behavioural level there is an apparent choice of AD/HD children to respond to immediate events over other possibilities. How does DA availability affect this? The answer here requires an understanding of what may be happening at the synapse of an AD/HD patient with/ without medication (figure 3). Normally in the basal ganglia (in contrast to

mesocortical regions) the ratios of DA, DAT and receptor densities are similar and the function of DAT is likely to be a major contributor to DA signalling (133). Efficient DAT limits the duration of DA induced synaptic activity – at low DA levels it stimulates DA release, at higher levels the DA D2 autoreceptor attenuates release (133). One would presume that psychostimulants are efficacious, as the first of these two processes is impaired. But this need not mean that the DA system is hypoactive. The increase could activate the D2 autoreceptors to reduce the (over-)release of DA especially that associated with the neural impulse. Indeed methylphenidate also reduces the rate of spontaneous firing in mesolimbic neurons (197). Thus the overall effect of treatment could be to increase tonic, but to decrease phasic DA release (198). This would seem to fit the data from Schultz's monkeys (194). He related a fast phasic component of the neural response to reward prediction: this may be too strong in AD/HD and should be attenuated to allow delayed behavioural response. Grace (198) suggested that through delayed development the reduced cortical glutamatergic input to the accumbens would lead to a hypoactive DA system. This proposal has been incorporated in the dynamic developmental model of Sagvolden (96).

In adult subjects with AD/HD striatal DAT binding was reported to be unusually high (a SPECT study), and was reduced by nearly 30% after a month of methylphenidate treatment (199). This supports the notion (above) that tonic levels of DA would increase, as confirmed for normal adults (200). Interestingly, in animals, co-administration of methylphenidate with nicotine – there are presynaptic acetyl-choline receptors on mesolimbic neurons – increased DA levels in an additive manner (201). This may provide a basis for apparent attempts at self-medication through cigarette smoking. Important for the distinction between the function of tonic and phasic activity, and its behavioural effect, Volkow's PET studies in humans show that methylphenidate-induced increases in DA are associated with an enhanced perception of a stimulus as salient (202). While such perception is clearly relevant for the interest in and motivation generated by such stimuli, it relativises the emphasis placed on mesolimbic reinforcement processes in the direction of the attentional mechanisms I have emphasised.

There is evidence for genetic variation in the production of more and less efficient DAT. The 10-repeat allele for DAT (3' variable number tandem repeat polymorphic site in 3' region of the gene SLC6A3) is reportedly over-active. To obtain this beneficial behavioural, attentional and biochemical response to methylphenidate it is advantageous **not** to be homozygous for the 10/10 repeat allele of DAT (203-208) – even though the EEG of homozygotes is somewhat normalised after treatment[6] (206). Although there is modest reason for suggesting a biased transmission of the 10/10 variant in AD/HD (210, 211), many studies do not find this – implying that we should be looking for other types of DAT variant.

As suggested above there is evidence for the involvement of the ventral striatum, thalamus and orbital-frontal cortex in discriminating reinforcement contingencies (or their saliency) in normal subjects (212)

[6] The opposite effect (increased theta power) on the magnetic form of the EEG after methylphenidate treatment was reported for a group of ADHD patents who had not been genotyped (209)

and that the 10/10 allele is associated with size reduction of the nearby caudate nucleus (128). However, there is sparse evidence that methylphenidate is associated with changes of the aversion to delays. Yet, we have long known that the steep reinforcement gradient shown by the spontaneously hypertensive rat model of AD/HD is improved after methylphenidate treatment (213). Immediate reinforcement was less effective and responses for delayed reinforcement were strengthened. The same effect of treatment was reported from a study of adults with a history of criminal behaviour (214). One presumes that the weak signal provided by a cued delay of reinforcement is amplified by the drug's effect on DA release. This seems to be supported by another PET study of normal adults from the Volkow team (215) showing that while the sight of food elicited no change in the dynamics of DA activity, there was a major response if the subjects had received a prior dose of methylphenidate. However, the apparent support from animal work is a bit difficult to reconcile with other rodent studies showing that chronic treatment in the pre- and peri-adolescent period resulted in less interest in natural rewards [e.g. sucrose, novelty and sex: (216)]. This qualification and the interpretation of Volkow's data would seem to put emphasis on the processing of the 'signal' rather than on incentive and motivation.

Mesolimbic Pathway (5-HT)

The previous section introduced the interactions of 5-HT with DA in regions innervated by the mesocortical projections. Such interactions are relevant in areas innervated by the mesolimbic system, and do concern the questions about impulsivity, of reinforcement mechanisms and motivation just addressed.

In AD/HD children cognitive impulsivity measured by a reduced probability of inhibition in the stop-task, is associated with decreased affinity (increased Kd in platelets) of the 5-HT transporter (22): (figure 4)[7]. With regard to the reinforcement mechanisms, stimulants like amphetamine (therapeutic in AD/HD) and cocaine act presynaptically on DA transport. Both alter 5-HT dynamics. Indeed if the DA transporter is knocked out in rodents reinforcement measured by cocaine administration (217) or conditioned place preference to amphetamine (218) remains, - until a 5-HT_{1a} antagonist is administered. Further, the sensitivity to reinforcement administered by intracranial self-stimulation to the hypothalamus is increased by treating the median raphe nucleus with a 5-HT1a agonist (219). Interactions between 5-HT and DA systems are central to considerations of cognitive impulsivity and the associated evaluation of reinforcement.

There is a large body of animal research that clearly shows the involvement of 5-HT interactions with DA in the mediation of the mechanisms underlying the preferred choice of AD/HD children for receiving immediate rather than delayed rewards. Measures taken with a dozen agents blocking NA and 5-HT uptake (but not DA uptake) show that there is an increased efficiency for obtaining water presented on a schedule of differential reinforcement at low rates of response [DRL: (220, 221)]. A similar effect was seen in young adult

[7] Cognitive impulsivity should not be confused with the poor control of aggressive responses, often seen in ADHD children especially those with comorbid conduct disorder. For disruptive behaviour the association with the affinity of the transporter was the opposite (figure 4), consistent with a large literature on the role of 5-HT in aggression (22)

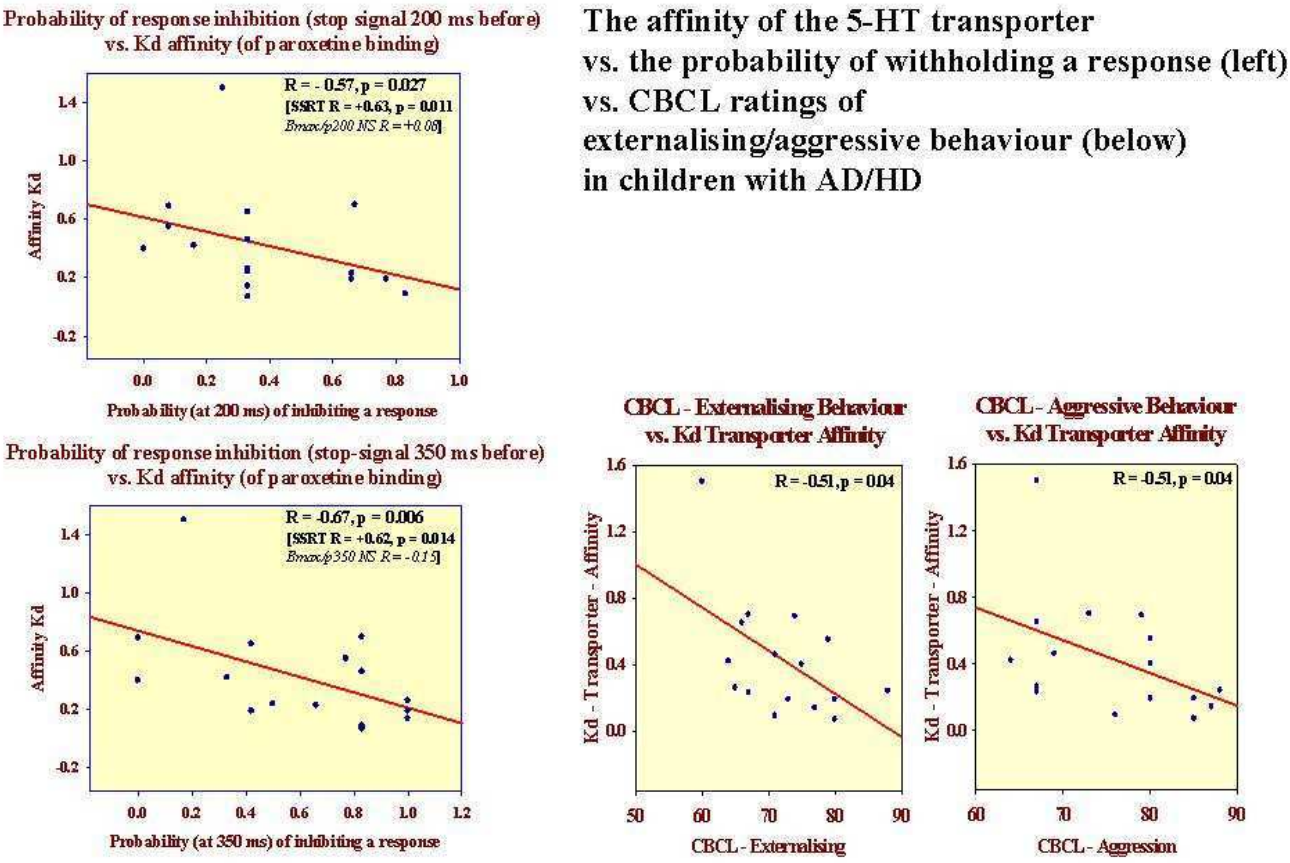

Figure 4

The relationship of the affinity (Kd) of the 5-HT transporter on platelets sampled from children with AD/HD with (left) their ability to withhold response if required on the Stop-task (stop-signal reaction time SSRT) – the lower the probability of inhibiting a response (i.e., the more impulsive) the higher the Kd (lower affinity: Bmax was unrelated). On the right the reverse relationship between increasing Kd and more aggressive behaviour is shown. [Modified after (22) and reproduced with the permission of Taylor/Francis].

criminals given paroxetine while performing a task where a short delay resulted in a small reward, but a longer delay gave more reinforcement (222). [It may be noted that sub-chronic paroxetine down regulates pre- and post-synaptic 5-HT1a sites in normal young adults (223)]. In confirmation, enhancing activity at the HT1a sites in animals leads to problems with delaying response for reinforcement (224, 225). Enhancing activity at HT1b sites attenuates the effects of psychostimulants like amphetamine in decreasing impulsivity and promoting responses to targets (226), while HT2 *antagonism* may also lead to impulsive responding (227). Comparison between animals bred for high or low sensitivity to 5-HT1a stimulation showed the latter with high response rates, and low reward rates on a DRL schedule (228): these effects were

improved with reuptake inhibitors. Reduced 5-HT activity promoted the selection of the delayed but larger reward (229, 230). Recently thinking (and experiment) about these mechanisms led to the suggestion that while DA systems should be active during behavioural decisions requiring effort and concerning delay, 5-HT systems were *needed* for the latter (231).

Thus, overall, there is reason to believe that 5-HT plays a marked role in the sensory, reinforcement, inhibitory and motor processes that are disturbed in AD/HD. At least in relation to 5-HT activity, the DA system seems to be hypoactive.

The status of peripheral and central nervous monoamine systems:

Measures of the elimination of monoamine metabolites are indirect indicators of transmitter activity. It is difficult to identify the sources of these metabolites. But it is of both basic and clinical interest that there is some broad support for the relative activities between the monoamines, and some associations for these ratios with measures of symptoms or cognitive activity in young subjects with or without AD/HD.

NA metabolism:

Levels of the metabolite MHPG (3-methoxy-4-hydroxyphenyl glycol), possibly an indicator of resting NA metabolism, are reported to be unusually low in AD/HD in 8/13 studies (59). Raised levels of other metabolites such as NMN (normeta-nephrine) have been reported, possibly reflecting increased sympathetic activity (17, 179), as associated with the stress of a cognitive task (17, 232). Sub-chronic treatment with methylphenidate often results in further decreases of MHPG in peripheral catchments (233-238) that correlate with improvements in symptom ratings (237, 239). Speculatively, this may reflect a reduction of NA overflow resulting in the better control of DA/5HT interactions via the high affinity alpha-2 than the alpha-1 site that is more closely related to activity in stressful situations.

DA metabolism:

Pharmacological blocking of peripheral catecholamine breakdown shows that 15-20% of HVA may have a central origin. As a group levels are reported as normal, sometimes a bit low in CSF (240), plasma (241) and urine (235, 242). Psychostimulant treatment tends to lower HVA excretion (in urine, plasma and CSF), if not quite to the same extent as the effect on MHPG (179, 233, 242, 243). Shekim et al., (235, 236) reported a rate-dependent effect with high levels being lowered and low levels raised. Down-regulation has been reported to relate to decreases of symptoms, more especially for measures of hyperactivity than of attention (162, 240, 241, 244). Together these data suggest that in comparison with NA metabolism the DA system is relatively hyperactive (165), even if some indicators suggest that DA metabolic activity is lower than normal. For example, Konrad (17) reported that impulsive errors of commission on a CPT-ax task related to rates of eye-blinking, and hence indirectly DA activity. Further, signal detection measures on a test of sustained attention (CPTax) were inversely related to HVA in normal children: no such relationship was found in age-matched children with AD/HD (16).

5-HT metabolism:

A markedly lower ratio of DA to 5-HT metabolites (HVA/5-HIAA) reported in AD/HD subjects would be consistent with slightly lower DA and higher 5-HT metabolism (165). But this result has not been supported in all samples (167, 245).

However, the increased 5-HIAA levels reported were shown to correlate closely and inversely with two quite separate measures of attentional ability, namely conditioned blocking and sensitivity (d-prime) on the CPT-ax task (16, 164). These results along with those for the stop-task (see figure 3) are consistent with an over-availability of 5-HT in the synapses of children with AD/HD.

Could there be a simple explanation for the proposed relatively hyper-serotonergic (*vs*. DA) situation? Uzbekov (179) proposed one possibility. His laboratory found that while stimulant treatment (sydnocarb) reduced the high levels of 5-HIAA, N-methyl-nicotinamide (N-mna) levels rose. N-mna is the end product of the alternative metabolic pathway for the 5-HT precursor L-tryptophan. One may entertain the possibility that over activity of the indoleamine was pharmacologically diverted to an alternative metabolic route. This would be consistent with a psychostimulant induced reduction of 5-HT levels (246). The hypothesis is open to test.

Conclusions:

The diagnostic manuals maintain that AD/HD incurs differentially a broad range of cognitive (inattention), motor (hyperactive) and impulsive (response inhibition) problems. The core of this was described some 50 years ago (247). The bases for these and related problems lie along a cerebellar – pontine/mesencephalic – cerebro-cortical axis [cf. pathophysiological findings, (248)]. Recent experimental and pharmacological work points to a large contribution from the monoaminergic pathways originating in the mid/hind brain to the dysfunctions in the target areas innervated by dopamine (DA), noradrenaline (NA) and serotonin (5-HT). A significant proportion of these (dys)functions can be attributed to executive processes, the evaluation of stimuli and the reinforcement potentially associated with these events. Monoamine activity is discussed within the context of a dual-pathway theory of AD/HD function (92). In this context mesocortical contributions to neuropsychological performance are described here for NA (with respect to DA) and mesolimbic contributions to reinforcement-related processes are described for 5-HT (with respect to DA). To divide the roles of the pathways in this way is useful but does tend to over simplify. Thus, different forms of impulsivity depend on mesolimbic and on mesocortical interactions. To summarise in terms of DA activity being proportionately higher than that for NA or lower than that for 5-HT has a degree of validity but is a generalization masking some of the details of the mechanisms involved. The realisation of cognitive process in the form of adaptive behaviour necessarily incurs additional local GABAergic feedback, glutamatergic cortico-striatal integration and moderation by cholinergic input.

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