Dopamine-serotonin interactions in attention-deficit/hyperactivity disorder (ADHD)

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Abstract:

Poor control of attention-related and motor processes, often associated with behavioral or cognitive impulsivity, are typical features of numbers of children and adults with attention-deficit hyperactivity disorder (ADHD). Until recently clinicians have seen little need to improve on or add to the catecholaminergic model for explaining the features of ADHD. Recent genetic and neuroimaging studies however provide evidence for separate contributions of altered dopamine (DA) and serotonin (5-HT) function in this disorder. Genetic studies imply that for both DA and 5-HT systems variants may frequently occur in ADHD for neurotransmitter uptake, synthesis and breakdown functions. The separate distributions in the brain of mesolimbic DA transporter and mesocortical DA D4 binding sites, both strongly implicated in ADHD, draws attention to potentially differential contributions from the 5-HT system. However, the evidence here points less towards an anatomical differentiation, as towards one in terms inhibitory/facilitatory pre/postsynaptic location of receptors in the 5-HT_1 and 5-HT_2 families. While the monoamine metabolite levels excreted in ADHD are often correlated, this may well flow from a starting point where 5-HT activity is anomalously higher or lower than the generally lower than normal levels for DA. It appears that perhaps both situations may arise reflecting different diagnostic subgroups of ADHD, and where impulsive characteristics of the subjects reflect externalizing behavior or cognitive impulsivity. For these features there is clear evidence that DA and 5-HT neuronal systems can and do interact anomalously in ADHD at the level of the soma, the terminals and at a distance. Interactions mediated by macroglia are also likely. However, it remains difficult to ascribe specific mechanisms to their effects (in potentially different subgroups of patients) from this relatively new field of study that has as yet produced rather heterogeneous results.

Key words: Attention, ADHD, dopamine, genetics, glia, impulsivity, prefrontal cortex, serotonin, venlafaxine

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COMT, catecholamine-ortho-methyl transferase; CPT, continuous performance task; DA, dopamine; DAT1, dopamine transporter; DDC, dopa decarboxylase; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; IFN-γ, gamma-interferon; IL-6, interleukin-6; NA, noradrenalin; SERT, serotonin transporter; SNP, single nucleotide polymorphisms; TGF-β, transforming growth factor-beta; TPH, tryptophan hydroxylase; VNTR, variable number tandem repeat;

1. INTRODUCTION:

1.1 The clinical problems of ADHD:

The principle domains of dysfunction in this disorder are reflected in the name attention-deficit hyperactivity disorder (ADHD) and may be found in nearly 10% of children world-wide (Faraone *et al.*, 2003). It is widely agreed that the constituent characteristics represent extremes of features normally distributed through the population. Indeed, the high heritability of the disorder at c. 70% (Faraone *et al.*, 2005) provides a basis for the genetic strategy of investigating risk factors, known as the quantitative trait locus approach (Asherson and Image Consortium, 2004). This has the potential to link the categorical disorder to continuously distributed traits associated closely with the underlying genetic liability in the general population.

There is a subtype of ADHD where the domains of overactivity, restlessness and behavioral impulsivity predominate (hyperactive-impulsive or ADHDhi), and another, an inattentive subtype (ADHDin), where poor executive attention and cognitive impulsivity predominate. But for most of the cases seeking professional help these features are found together in the combined type (ADHDct). These features are not expressed all the time. The DSM IV manual (American Psychiatric Association) describes them as "often present": in laboratory studies one notes a high intra-individual variability in the measures taken (Scheres *et al.*, 2001; Russell *et al.*, 2006). In all clear diagnoses a clinical impairment is noted.

Some cases are markedly withdrawn showing low self-esteem, others show frequent outbursts of affect, many are characterized by both of these 'internalizing' and 'externalizing' traits, and most have problems in social and academic environments. Frequently these problems are diagnosed as comorbid (e.g. oppositional and conduct disorder). Onset is usually in mid- or early childhood and affects boys more than girls [c. 3-5 to 1 (Buitelaar *et al.*, 2006)]. In about a third of cases the disorder persists into adulthood and the gender ratio evens out (Biederman *et al.*, 2004).

1.2 Dopamine not serotonin dysfunction?

Consensus suggests that in one form or another dopamine (DA) activity is lower than normal in children and adolescents with ADHD (Levy, 2004; Iversen and Iversen, 2007). Thus, based on the knowledge that intimate interactions between DA and serotonin (5-HT) occur widely through the mammalian brain (see previous chapters) one would intuitively expect – as cause or effect – that there would be some changes in the activity of 5-HT in cases with ADHD. One should first ask why this idea has to date had little resonance with the psychologists and psychiatrists who study ADHD.

Key evidence for the view that central 5-HT activity is irrelevant to explanations of ADHD derives from the success of the medication usually prescribed. Long- or short-acting forms of methylphenidate improve the problems of 60-70% of both younger and older ADHD patients (Wigal *et al.*, 2004; Biederman *et al.*, 2007a). Merely the domain of the problem (e.g. restless motor activity, poor social interactions and attention-related cognition) is differentially sensitive to dose (Pelham and Murphy, 1990). The overall proportion of patients improving with treatment rises to around 80% if another psychostimulant such as amphetamine is considered (Committee on children and disabilities and committee on drugs, 1996). Methylphenidate inhibits the reuptake of DA and noradrenalin (NA), but has no *direct* effect on 5-HT (Leonard *et al.*, 2004). The present discussion does not consider further the role of NA activity

that undoubtedly also contributes to cerebrocortical dysfunction in ADHD (Oades, 2005). Successful medication is apparently not acting on 5-HT systems and the clinician is happy with such a good response rate to these agents. Certainly the dogma, promulgated in older reviews (Oades, 1987; Zametkin and Rapoport, 1987), has long been that one does not need to consider 5-HT to explain clinical observations, or the results of laboratory examinations of ADHD behavior.

However, the argument for the catecholamine and against the 5-HT contribution to ADHD is somewhat superficial. It would seem important to seek an explanation for why around 30% of patients are non-responders, and seek reasons for why a large proportion of 'responders' show far less than a 50% improvement. Most children with ADHD show little or no improvement of academic performance or social function (Abikoff *et al.*, 2004; Gualtieri and Johnson, 2008). Indeed the striking improvement seen after methylphenidate treatment in the NIMH multimodal treatment study over the first year of the study dwindled to the very modest levels recorded after intensive psychotherapy over two to three years (Jensen and Arnold, 2004). In seeking an explanation it is appropriate to suggest that 5-HT or a quite different component of CNS function may be playing a significant role?

2. Evidence for an altered dopaminergic and serotonergic contribution to ADHD:

2.1 Dopamine (DA)

First, it is useful to recall briefly, good evidence that the activity of DA and 5-HT are associated with the expression of ADHD when considered separately. Investigations to provide direct evidence of neurotransmitter involvement in ADHD have usually not considered the role of more than one transmitter. These studies and indirect evidence for interactions are discussed in section 3. Examples of key evidence focusing on DA (here) and 5-HT (section 2.2) are selected from the fields of neuroimaging and genetics.

Volkow and colleagues (2007b) describe a comparison of D2/D3 receptor availability in medication-naïve adults with ADHD with healthy subjects using positron emission tomography (PET) and the D2 ligand [^{11}C] raclopride. They recorded a lower availability of binding sites in the left caudate nucleus on placebo. After methylphenidate treatment there was a blunted bilateral response in the striatum that extended to the limbic region of the amygdala and hippocampus. Similar PET/SPECT studies report a decrease of the DA transporter in the basal ganglia and thalamus (Hesse *et al.*, 2006; Volkow *et al.*, 2007a)). [Volkow relates how recent replications have resolved some of the differences with earlier conflicting reports.] Of great interest is the extension of the findings of 'hypodopaminergia' from striatal to both limbic and to thalamic regions (figure 1). In addition to the much-studied striatum, the thalamus is a major component of the fronto-striatal circuits where DA-modulated dysfunction is often invoked as a basis for cognitive problems in ADHD (Swanson et al., 2007) and where the DA transporter (DAT) is normally so abundant (Telang *et al.*, 1999; Garcia-Cabezas *et al.*, 2007), figure 2). It may be noted that the usually extrasynaptic locus of DAT is here well suited to control the influence of DA on the moderate to dense 5-HT innervation of the thalamus from the raphe nuclei (Morrison and Foote, 1986; Vertes, 1991).

The above reports are of particular interest as the authors related the neurochemical PET changes registered, with some of the clinical features of their patients. For example, the blunted limbic (raclopride-binding) response to

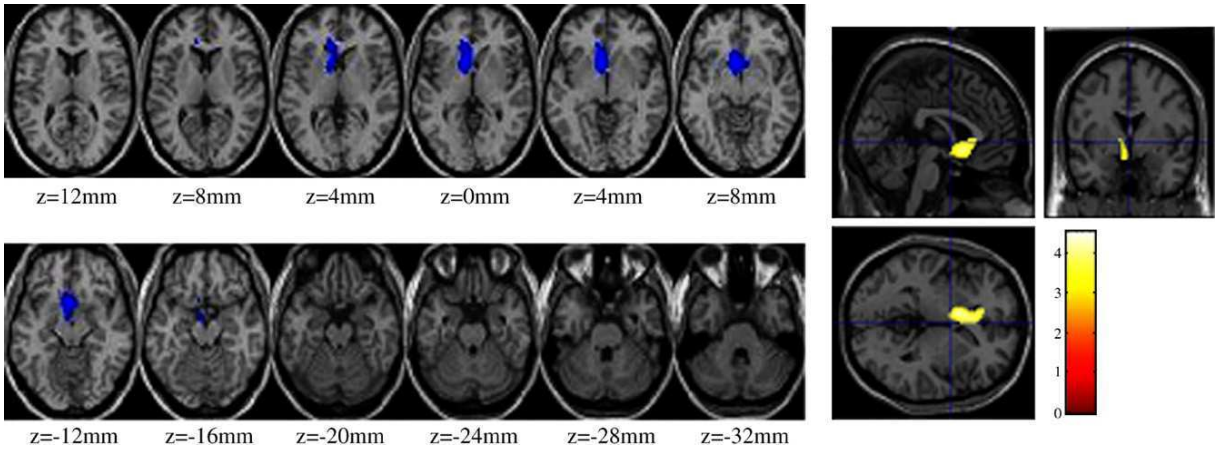
Figure 1:

Regions where PET measures of DAT levels differed between adults with/without ADHD (A) and the relationship of inattention severity to DAT level in these subjects (B)

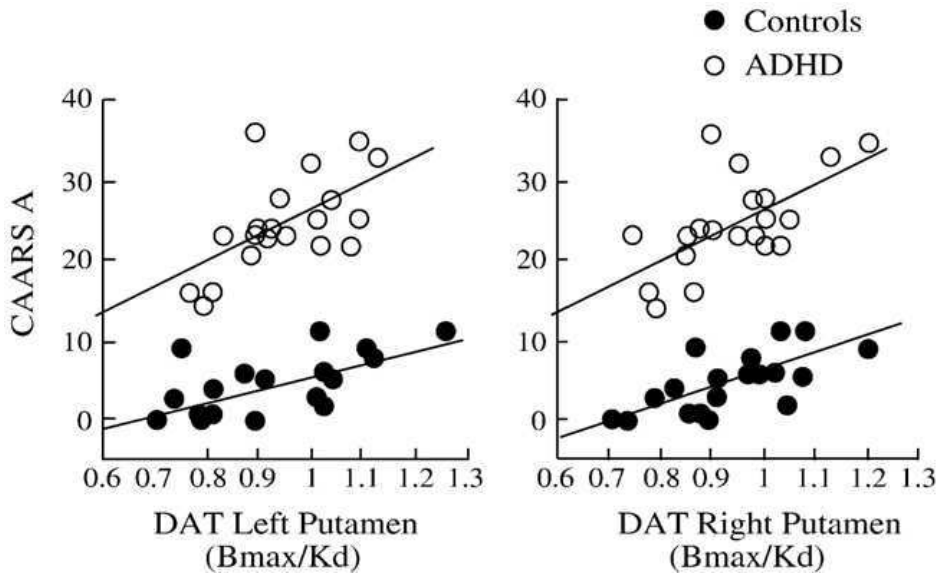
A/ Regions centred on the nucleus accumbens and hypothalamus where levels of DAT were significantly higher in healthy controls than adults with ADHD

B/ Regression slopes between DAT availability (right and left putamen) and ratings of inattention (Conners scales) in adults with ADHD. They show severer symptoms at any given level of DAT in the patients. (modified after Volkow *et al.*, 2007a) and reproduced with the permission of Elsevier)

A/



B/



medication, and the DAT1 binding in the putamen were significantly related to ratings of inattention on the Conners scale (Volkow et al., 2007a, b: figure 1).

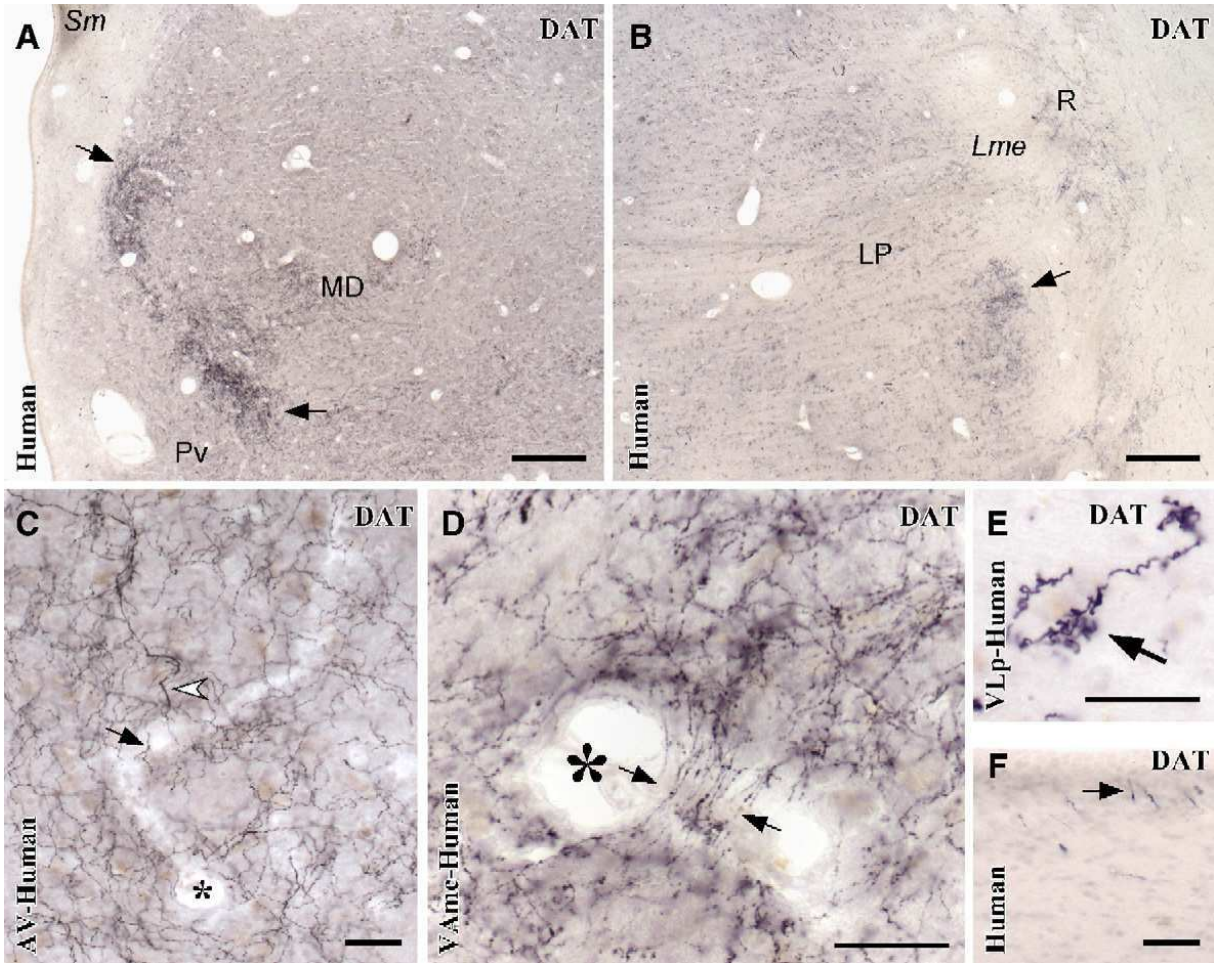
The current state of genetic studies does not offer much support for unusual polymorphisms affecting D2/3 receptor function (but see Nyman *et al.*, 2007), but does imply that variants of the DA D4 receptor, abundant in mesocortical regions, and the DA transporter (DAT1), abundant in mesolimbic/striatal regions, are associated with features of ADHD. The former (D4) seems to be important for the

"inattentive" and the latter (DAT1) for the "hyperactive-impulsive" part of the clinical spectrum of ADHD (Diamond, 2007). [Note: DAT1 removes most of the unused extracellular DA in subcortical regions, whereas in the cortices >60% of the DA is removed by the catabolic enzyme COMT.]

Central to numerous studies of the DAT1, has been the association with ADHD of the 10-repeat-allele of a variable number tandem repeat (VNTR) in the 3'-untranslated region of the DA transporter gene. Some recent meta-analyses have played down the strength of this association. However, the reason lies with a confound usually overlooked in most reports, namely that the 10-repeat allele concerned in fact tags a nearby functional variant, the 6-repeat-allele of another VNTR in intron 8. This has been replicated in the IMAGE cohort that now includes a total of 1159 children with ADHD (Asherson *et al.*, 2007).

Figure 2:

Dense and uneven immunolabeling of DAT in the human thalamus is shown, and lies in proximity to the innervation from the raphe nuclei (see text). DAT labeling **A/B** in associative medio-dorsal (MD) and lateral posterior (LP) nuclei (calibration 400 μM), **C/D** in limbic antero-ventral (AV) and motor ventro-anterior (VAmc) and posterior ventrolateral (VLp) nuclei (calibration 40 μM): modified after Garcia-Cabezas et al., 2007 and reproduced with the permission of Elsevier.



2.2. Serotonin (5-HT)

Few have seriously investigated the putative involvement of 5-HT in ADHD. Thus, there are few studies with neuroimaging techniques to compare the potential contribution of 5-HT activity with that described for DA in the previous section. Hesse and colleagues (2006) report no evidence for unusual binding characteristics of the 5-HT transporter (SERT) in their SPECT study (^{123}I-FP-CIT**)** of the midbrain and brainstem of adult ADHD patients. However, (Riikonen *et al.*, 2005) used the radioligand ^{123}I-labelled nor-CIT, which specifically labels SERT with a 10-fold higher affinity than the DA transporter, in their study of children with ADHD and fetal alcohol syndrome. They reported significantly less binding (25%) in the anterior cingulate cortex, but found no reductions in the temporal cortices or in the midbrain. More studies are required to avoid the confounds of comorbidity, preferably with the use of high affinity ligands that are necessary to provide clear results (Elfving *et al.*, 2007).

Other approaches indeed suggest that some aspects of SERT activity do not function well in ADHD. For example, (Oades *et al.*, 2002) describe an increased affinity (reduced Kd) for platelet SERT-binding measured with paroxetine in children with ADHD. [The platelet model appears to mimic the situation in the CNS (Cheetham *et al.*, 1993).] This was associated with the characteristically poor attention and performance shown on the stop-signal task that was also correlated with ratings of distractibility and impulsivity. This is illustrated in figure 3, which also shows the opposite relationship observed for ratings of (impulsive) outbursts of aggression. Much earlier reduced binding of ^{3}H-imipramine to NA and 5-HT uptake sites was reported for prepubertal children with ADHD and conduct disorder (Stoff *et al.*, 1987). Further, several genetic studies claim that short or long forms of the transport promoter region that show reduced/enhanced transcriptional efficiency (respectively) are preferentially transmitted in ADHD (Biederman and Faraone, 2005; Curran *et al.*, 2005; Li *et al.*, 2007). However, some recent negative findings (Wigg *et al.*, 2006; Guimaraes *et al.*, 2007) clearly underline the need to differentiate between subgroups in future investigations. A recent brief review of the heterogeneous genetics literature on other features of the 5-HT system (Oades, 2007) concluded that there was tentative support for association of alleles associated with the 5-HT_{1B} receptor in cases of the predominantly inattentive subtype, and with the 5-$HT_{2A/C}$ receptor(s) in subjects showing more hyperactivity and impulsivity. This review also describes evidence for inefficient 5-HT synthesis in ADHD that relates to transmission of a variant for the enzyme tryptophan hydroxylase (TPH2).

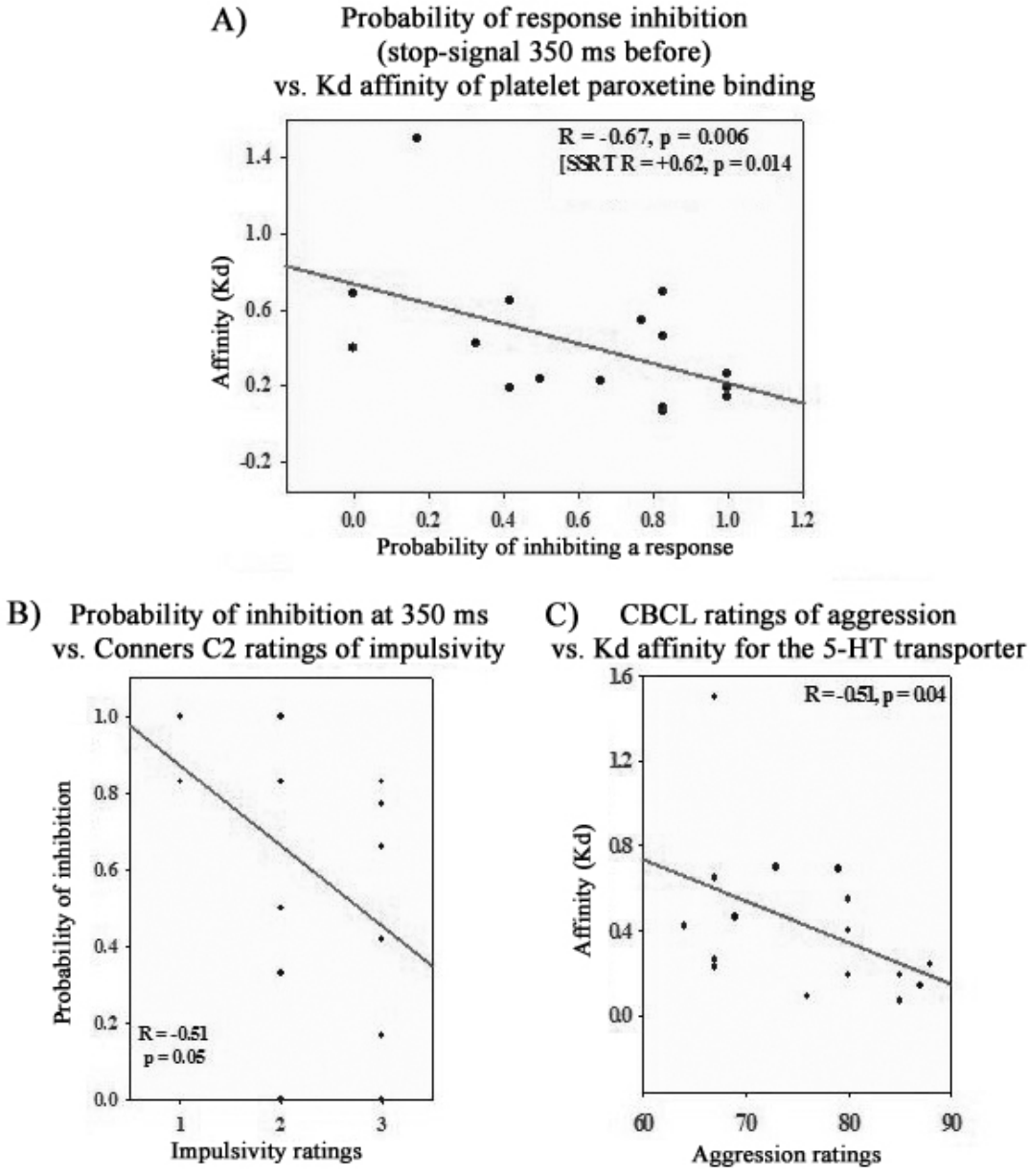
3. Putative dopamine and serotonin interactions in ADHD

3.1 Introduction:

The overlap of ascending 5-HT and DA projections to both subcortical and cortical territories, like the putative roles of 5 types of DA receptor and perhaps 22 types of the 5-HT receptor are discussed in detail elsewhere in this volume (Di Matteo, 2008; Mengod, 2008; Steinbusch, 2008). However, as yet, the only functional outcome one can discuss in the context of ADHD is that the numerous and varying types of interaction appear to have an effect, and that the nature of this effect can be described merely on a rather large scale with poor resolution. As a contribution of 5-HT to ADHD has largely been ignored, there is a near absence of studies designed to examine its potential specific interactions with DA. Thus this review largely focuses on those studies

Figure 3:

In children with ADHD, (**A**) the affinity (Kd) for 5-HT uptake in platelets *vs*. the probability of response inhibition on the stop-task (stop-signal 350 ms prior to the mean response time), (**B**) the probability of stop-task inhibition *vs*. the ratings of impulsivity on the Conners' scale, and (**C**) the affinity of 5-HT uptake *vs*. Child behavior checklist (CBCL) rating of aggressive behavior (Modified after Oades et al., 2002 and reproduced with the permission of Taylor/Francis).



that have at least considered both transmitters: where a change of activity reflecting both monoamines has been recorded, an interaction is inferred.

Nonetheless such putative interactions are based on solid anatomical evidence for the frequent convergence of these two monoaminergic systems (Phelix and Broderick, 1995). It is perhaps useful in the following discussion to hold three categories or types of interaction in mind. At the level of the neuron or pathway, changes of DA activity can affect 5-HT responsivity (1), with inhibition in terminal regions (Consolo *et al.*, 1996; Di Matteo, 2008) or disinhibition at the autoreceptor

level (Mendlin *et al.*, 1999). Stimulation or blockade of 5-HT neurons can influence DA responsivity (2), especially though blockade or stimulation (respectively) of psychostimulant-induced release of mesolimbic DA (Porras *et al.*, 2002; Esposito, 2008). Alternatively, a functional interaction may occur at a distance, mediated by an intermediate neuron (3).

Some specific examples of these sorts of interaction are as follows. (1) Damage to DA systems in neonatal rats lead to a large increase of 5-HT release in the basal ganglia (Luthman *et al.*, 1989). (2) Blockade of 5-HT_2 binding sites leads to increased DA outflow as measured by PET records of raclopride binding in baboons (Dewey *et al.*, 1995). These examples illustrate the traditional view of the mutual inhibition of the activity of these two monoamines. As models they are both pertinent to potential explanations of the situation in ADHD (see impulsive cognition and aggression, above). This disguises the nature of other forms of interaction that occur in detail, and vary with the pre- vs. postsynaptic location of different types of receptor in cell-body (midbrain) or mesolimbic/cortical projection regions (review:(Millan *et al.*, 2007).

An important and significant example of influence "at a distance" (3) is the facilitation of ascending DA transmission via stimulation of 5-HT_{1b} receptors on GABA interneurons in the midbrain (Millan et al., 2007). But there are numerous other potentially significant "influences at a distance", as illustrated by the striofugal pathways to parts of the pallidum (Levesque and Parent, 2005). Not only can a major 5-HT input modulate the influence of DA activity directly in the organization of behavioral modules in the striatum, but it can also have a "second go" through the heavy innervation to the pallidum at the start of the final common pathway (Napier and Istre, 2007). Analogously, the motor cortices also receive a major input from 5-HT projections whose activity facilitates gross motor output (Jacobs and Fornal, 1995). Surprisingly, none of these features of CNS circuitry have received much attention in the context of the restlessness, hyperactivity and clumsiness often associated clinically with ADHD or in laboratory studies of impaired fine motor control (Meyer and Sagvolden, 2006; Rommelse *et al.*, 2007). An indication that there is a DA/5-HT interaction affecting motor control is that the ratio of their metabolites measured in CSF has been reported to correlate positively with ratings of motor activity (Castellanos *et al.*, 1994). However, in this particular case inferences should be qualified by noting that the relationship reported was strongly driven by the DA metabolite.

The concept of influence at a distance has widespread implications when one considers the 5-HT innervation extending from the midbrain raphe nuclei to a series of subcortical regions (e.g. habenula) or cortical territories (e.g. cingulate) that then feed back directly to the origin of DA pathways in the ventral tegmental area (Oades and Halliday, 1987). This principle also operates for regions innervated by DA.

3.2 Studies on both dopamine and serotonin in investigations of ADHD

3.2.1 Genetics:

Meta-analysis of genetic studies of ADHD has shown support, from at least three reports each (Faraone *et al.*, 2005), for an association between the disorder and variants of several DA and 5-HT receptors (D4, D5, DAT1, 5-HT_{1B} and SERT). Arguably, more important and relevant to the present consideration of DA/5-HT interactions are findings from within one large cohort [IMAGE, (Brookes *et al.*, 2006)]. This is because reports of associations with DA and 5-HT variants

within one cohort provide a good starting point for eventually demonstrating their joint importance in individuals. The IMAGE team found adjusted gene wide significance for variants affecting DA uptake (DAT1), 5-HT synthesis (TPH2) and monoamine breakdown (MAO-A) based on 674 families with 776 child and adolescent cases of ADHDct. Nominal significance extended to D4, 5-HT_{1E}, and dopa decarboxylase (DDC) that is involved in both DA and 5-HT synthesis. In this study of 51 candidate genes involved in monoaminergic transmission, fatty acid synthesis and circadian rhythms, nominal significance extended to 12 other genes less relevant to this discussion, but importantly not to the remaining 33 genes. Considering that a study of the heterogeneity in the IMAGE population demonstrated the appropriateness of the North European contribution to this cohort (Neale *et al.*, 2007), there is a reasonably firm basis for claiming that aspects of both 5-HT and DA activity contribute to the variance in ADHD. Indeed our current family based association analyses of impulsivity in the IMAGE cohort suggest gene-wide significant associations for 5-HT_{1E} (and adrenalin synthesis) alongside nominal indications of the relevance of variants for 5-HT_{2A}, TPH2, D4 and 5-HT_{1B}, TPH2, D1 genes in behavioral and cognitive impulsivity, respectively (in preparation). However, only now are various laboratories tackling the nature of the dependence of an individual phenotype on interactions between 5-HT and DA.

Broadly supportive of part of the IMAGE study is the recent report from (Ribases *et al.*, 2007) on adult and childhood cases of ADHD. They claim an association with ADHD for certain SNPs (single nucleotide polymorphisms) in the genes controlling expression of DDC (chromosome 7), the 5-HT_{2A} receptor (chromosome 13) and the X-linked monoamine oxidase (MAO-B). Corrected significant results for DDC and 5-HT_{2A} were based on 451 child and adult cases and for MAO on 188 adult cases. This is intriguing as DDC and MAO-B are involved in the synthesis and breakdown respectively of *both* DA and 5-HT. Indeed there is some marginally significant support elsewhere for the DDC result with variants reported from a similar location (Hawi *et al.*, 2001). Neuroimaging studies also offer some support for anomalies in monoamine synthesis involving DDC. PET measures of fluorodopa, where interregional ratios index DDC activity, were reported to be reduced in both adult and childhood ADHD cases, albeit in different regions. Nonetheless these indices of DDC activity related to diagnostically relevant features, namely, the behavioral and hyperactive symptoms (Ernst *et al.*, 1998; Ernst *et al.*, 1999). Using a simple additive-model, Ribases et al. estimated that the combined effect of their 3 risk haplotypes contributed 5.2% of the adult ADHD phenotypic variance and the DDC and 5-HT_{2A} genetic variants accounted for 2.3% of child ADHD variability.

Few studies have looked for an association of MAO-B with ADHD, and these have found no association (Domschke *et al.*, 2005). However, this region on the X chromosome bears further study as there is an extensive overlap for sequences determining MAO-A and MAO-B. A number of polymorphisms for MAO-A and its promoter region have been examined and there are several reports of preferential transmission of longer, active and shorter, less active forms, depending on the putative etiology of the types of patient studied (Oades, 2007).

In the current context, the finding of the over-representation of a specific 5-HT_{2A} haplotype (G-C-C) in adult and child-hood cases of the ADHDct subtype (Ribases *et al.,* 2007), is of special interest

as this receptor type is frequently located on DA neurons. While at least 5 other studies have not been able to find associations with ADHD for several variants affecting this receptor, there are a large number of SNPs available for study. An association with impulsivity on the Barratt rating scale in alcohol dependent patients has been described (Preuss *et al.*, 2001). Indeed, (Reuter *et al.*, 2006) report that one allele (T102C) was significantly associated with ratings of hyperactivity and impulsivity in a group of healthy adults (see also (Nomura *et al.*, 2006). This is intriguing as in the same cohort there were strong correlations for the met/met allele of the enzyme COMT (active in mesocortical DA breakdown) with hyperactive and impulsive as well as inattentive subgroups. This implies potentially a separate, as well as a joint, influence of the two monoamines on the phenotype. These finding are of further interest firstly because such ratings could apply to ADHDct *and* ADHDhi subtypes, secondly the association with ADHDhi provides an interesting counterpart to associations of the 5-HT_{1B} receptor with the ADHDin subgroup (Hawi *et al.*, 2002; Smoller *et al.*, 2006; Oades, 2007), and thirdly, the results remind one of the blockade by 5-HT_{2A} antagonists of hyper-locomotion induced by DA stimulation in animals (O'Neill *et al.*, 1999; Porras *et al.*, 2002; Bishop *et al.*, 2005). The 5-HT_{1B} and 5-HT_{2A} receptors are contrasted here as animal studies suggest that, respectively, they are frequently presynaptic and inhibitory, and postsynaptic and excitatory in location and function (Millan et al., 2007).

A number of genetic studies have been directed to SERT, and in particular, have concentrated on long and short forms in the promoter region. This is also nominally of interest to this analysis of DA/5-HT interactions, as SERT is also capable of transporting DA. Indeed, genetically speaking all 3 monoamine transporters share a 50% sequence homology (Gainetdinov and Caron, 2003). Some (but not all) studies of SERT transmission have found associations of short (Li et al., 2007) and long variants in the promoter region (Kent *et al.*, 2002) or the 12 repeat allele in the intron 2 VNTR (Banerjee *et al.*, 2006) with ADHD expression. Oades (2007) suggested that the heterogeneity of results reported for these markers may reflect the need for defining more closely the subtype(s) and comorbidities expressed in the patients examined. For example, there is a well established relationship for externalizing behavior and conduct disorders often comorbid with ADHD with low 5-HT activity (Flory *et al.*, 2007; van Goozen *et al.*, 2007), platelet 5-HT uptake mechanisms (Stadler *et al.*, 2004) and long/short forms of the SERT promoter region (Cadoret *et al.*, 2003). Variations of some of these measures also seem to reflect social stratification and geographic origin (Manuck *et al.*, 2005; Li *et al.*, 2007). However, only the study from Schmidt *et al.*, (2007) has directly concerned the interaction with DA mechanisms. In their review of the literature they found that the presence of 1-2 copies of the short allele of the SERT gene and the long allele (7-repeat allele) version of the DA D4 gene predicted internalizing- and externalizing-related behaviors, respectively. In their own work they reported that normal 7 year old children with this genetic combination did indeed show more externalizing and internalizing behavior than children with any other combination of long and short alleles. In contrast, those children with the long SERT form, as well as the long DA D4 genotypes, had the lowest reported scores on internalizing & externalizing behaviors. Such an interaction suggests that the long SERT form could, in such circumstances, have a protective function.

Evidence from genetic studies is

starting to implicate 5-HT in neuroprotective and neuro-disruptive roles in ADHD. This could involve inhibitory and excitatory profiles under the control of receptors of the 5-HT_1 and 5-HT_2 families. But as the results as yet remain heterogeneous, one cannot rule out that both may be implicated through a common etiological problem with monoamine synthesis (cf. DDC and TPH2 results above). It is therefore natural that the present discussion should now proceed on to what is known about the activity of the neurotransmitter 5-HT itself.

3.2.2 Neurochemistry

It would be helpful for improving an understanding of the neurobiology of potential DA/5-HT interactions in ADHD to have measures of monoamine metabolism, or at least the results of pharmacological challenges on the release of hormones known to be controlled by these monoamines. These have naturally, for ethical reasons, been carried out rarely with minors, and the study of adults with ADHD remains in its infancy.

Nonetheless, a few studies are relevant for the interest in the 5-HT_{1B} and 5-HT_{2A} sites implicated above from genetic work. A group of children showing both oppositional defiance disorder as well as ADHD were given a challenge dose of sumatripan that is an agonist at several 5-HT_1 binding sites, especially the 5-HT_{1B} receptor (Snoek *et al.*, 2002). Compared to control children, the patients proved to be twice as sensitive to the challenge dose in terms of the growth hormone response. While this result implicates the 5-HT_{1B} site, it also suggests that the effect may have been achieved through excitatory postsynaptic sites rather than the more usual inhibitory presynaptic sites. In the second report Schulz et al. (1998) compared the cortisol and prolactin response to fenfluramine in ADHD children with and without fathers with alcohol problems (Schulz *et al.*, 1998). While both groups showed similar increases of prolactin, only the former risk group showed a marked increase in cortisol. The authors point out that as both 5-HT_2 and 5-HT_1 sites influence cortisol release, but only the 5-HT_2 sites affect prolactin, the conclusion must be that the 5-$HT_{2A/C}$ sites were not responding anomalously. Nonetheless considering that NA and 5-HT uptake blockade through desipramine can be clinically helpful (Gastfriend *et al.*, 1985; Donnelly *et al.*, 1986), and can also speed responses on a stop task and increase prolactin levels in ADHD children (Overtoom *et al.*, 2003), taken together the results do suggest that the 5-HT_2 site may influence processes normally approached by pharmacotherapy with methylphenidate alone.

Together, these studies support a potential involvement of 5-HT activity in ADHD, arguably by way of 5-HT_1 if not also via the 5-HT_2 receptor family, at least in a sub-group of patients. However, it is important to ask whether unusual levels 5-HT availability and metabolism at these receptors interact with DA (or vice versa) in ADHD. On the whole levels of the DA and 5-HT metabolites (homovanillic acid, HVA and 5-hydroxyindoleacetic acid, 5-HIAA) measured in the CSF of patients are inter-correlated. If symptoms are severe then HVA levels are often high. If levels are high they predict a good response to psychostimulant treatment and subsequently fall: falling HVA levels are followed by those for 5-HIAA (Castellanos *et al.*, 1996). HVA levels are not always high in ADHD, but low levels predict a poor treatment response. Low levels of 5-HIAA in the CSF are associated with episodes of aggression in children, adolescents (Kruesi *et al.*, 1990) and non-human primates (Higley *et al.*, 1996). Unexpectedly, these studies could report

no relationship for HVA with aggression. By contrast, in aggressive rats anticipating an encounter, microdialysis of mesolimbic regions demonstrated rising DA and falling 5-HT release (Ferrari *et al.*, 2003). However, of course, the rodent and primate situations are not exactly comparable.

It is interesting that the Castellanos CSF studies reported that there was no correlation between the monoamine metabolites they measured and indices of cognition and accuracy on a continuous performance task (CPT). However, they did find that the more controversial peripheral levels of the metabolites measured in urine correlated with those in the CSF. This lends support to the claim that urinary indices of monoamine metabolism are reflecting both somatic and brain sources. Here, in urinary sources the HVA/5-HIAA ratio was reported as being significantly lower in ADHD children than in healthy controls (Oades and Müller, 1997). The skew seemed to be driven by the higher levels of the 5-HT metabolite. Uzbekov, (2006) confirmed not only that HVA excretion was relatively low in children with ADHD, but that response to treatment with sydnocarb was accompanied by markedly reduced levels of 5-HIAA.

In summary it would seem that there is at least a subgroup of cases of ADHD where 5-HT systems are more active than normal and this can be partially corrected by stimulating DA activity. The discussion now proceeds to consider if these markers of the apparent involvement of 5-HT receptors and their activity in ADHD are associated with the activity of the brain and neuropsychological function where the DA innervation plays a role

3.2.3 Neuropsychology (Neuroimaging)

A recent review catalogued an increasing degree of influence of central 5-HT activity in ADHD across the field of attention-related processes from the treatment of salient stimuli (exogenous attention), over the inter-regional selective processes (endogenous attention) to cognitive impulsivity that reflects poor executive attentional control (Oades, 2007). It is, therefore, reasonable to examine first whether these processes reflect cognitive mechanisms that methylphenidate also influences through promoting catecholaminergic activity?

Certainly, on various versions of the CPT that reflect sustained attentional processes methylphenidate speeds responses, and the effect is blocked by antipsychotic agents (Levy, 1991; Levy and Hobbes, 1996). A contribution of DA is implicated. Slow latencies and more impulsive errors of commission in ADHD have been associated with the short allele of the DA D4 receptor (Manor *et al.*, 2002), a 148 bp allele of the D5 gene (Manor *et al.*, 2004), the 9 and 10-repeat alleles of the DA transporter (Loo *et al.*, 2003), and the highly active valine allele of COMT (Eisenberg *et al.*, 2003). In turn these have been associated with improvements following methylphenidate treatment (Manor *et al.,* 2002, 2004). Indeed CPT indices of inattention and impulsivity have been linked to PET measures of DA receptor sensitivity and availability when challenged with methylphenidate (Rosa-Neto *et al.*, 2005). [However, it is instructive to note that "improvement" does not mean that task performance normalized (Tucha *et al.*, 2005).] These reports complement the aforementioned contribution from 5-HT, where high activity (5-HIAA) impairs, and decreases relate to improved signal detection measures and performance (Oades, 2002; Overtoom *et al.*, 2003). Poor task performance can be associated with a variant of the TPH2 gene influencing 5-HT performance (-703 G/T: Reuter *et al.*, 2007). The potential for an interaction between these monoaminergic

systems is supported by improvements after methylphenidate treatment in those ADHD cases carrying risk variants of TPH2 for 5-HT synthesis, and who showed poor CPT performance in terms of speed of processing, reaction time variability and errors of omission (Manor *et al.*, 2008).

A recent report from Rubia *et al.* (Rubia *et al.*, 2007) concentrated on a set of tasks in which ADHD subjects have often been reported to make errors of commission. They found that cognitive impulsivity and an increased variability of response was the dominant overall result from administering a battery of 6 tasks where each tested a different aspect of inhibitory control in young people with ADHD. Not only do such tasks habitually engage frontal regions in the right hemisphere, but Rubia and colleagues (Rubia *et al.*, 2004) showed that decreased activity in these regions in healthy subjects who had taken a tryptophan depleting drink, was associated with trials on which they had difficulty to withhold a response as required. Several laboratories have found that after taking such a drink that restricts 5-HT synthesis, normal people do experience a range of difficulties in making stimulus-response associations, acquiring a reversal learning task and indeed show an impulsive style (Park *et al.*, 1994; Walderhaug *et al.*, 2002).

Delay avoidance or the preference for immediate, over delayed reward, even if it is larger, is a typical feature of childhood behavior and is exaggerated in many of those with ADHD: it has been described as the consequence of the failure of an *impulsive* child to engage effectively with delay-rich environments (Sonuga-Barke, 2005). Arguably, the phenomenon is related to the steeper reinforcement gradients attributed to ADHD children (Sagvolden *et al.*, 2005). That is, a stimulus and the appropriate response, have to occur closer together in time for an association to be acquired both in the animal model and for children with ADHD. There is wide agreement on the basis of animal studies, that the choice of, and switching to, an alternative stimulus for response depends on its salience, the perceived adaptiveness of a new situation or, very often, the anticipated reward: this involves bursts of DA activity (Oades, 1985; Goto *et al.*, 2007; Roesch *et al.*, 2007). It is less widely appreciated that to elicit such shifts requires region specific 5-HT participation (Winstanley *et al.*, 2006; van der Plasse and Feenstra, 2007). The role here is likely that of modulating the gain of the signal (Oades, 2006). While these authors emphasize mechanisms taking place in mesocortical projection regions (medial and orbito-frontal cortices: (Floden *et al.*, 2008) it may be noted that treatments that also influence subcortical regions will be involved in these DA/5-HT interactions. Thus, if the DA transporter is knocked out in rodents, reinforcement as measured by cocaine administration (Mateo *et al.*, 2004) or by conditioned place preference to amphetamine (Budygin *et al.*, 2004) remains, until a 5-HT_{1A} antagonist is administered. Indeed, stimulation of 5-HT_{2C} receptors actually attenuates the cocaine-induced release of DA from the rat's nucleus accumbens (Navailles *et al.*, 2008) while 5-HT_{1B} stimulation, as an example of gain modulation, enhances place preference responses for cocaine (Barot *et al.*, 2007). Clearly both DA and 5-HT systems were involved from the outset in mechanisms largely mediated by the mesolimbic system. Further, illustrating that the interaction can work both ways, Banks *et al*. (Banks *et al.*, 2008) reported that SERT availability is markedly increased in monkeys experienced in cocaine self-administration. These results could pertain to the vulnerability of ADHD patients for succumbing to substance misuse, where a bidirectional risk for

comorbidity is in fact apparent (Biederman *et al.*, 2007b).

However, underlying the reward aspects of risky decision making, there is an important component of information processing contributing to an "impulsive response style". Errors of commission made during a CPT task are regarded conventionally as a classic indicator of cognitive impulsivity. If children with ADHD persist in making such errors then one should consider whether there is anything amiss with their processing of their responses, and the feedback designating the response as an error. Some authors report that the increase in response latency normally seen in the first correct response after an error is often missing in those with ADHD (Schachar *et al.*, 2004), until treated with methylphenidate (Krusch *et al.*, 1996). It is then natural to ask about the Neurophysiolgical response in this situation. As yet, it is still too early to resolve the conflicting reports on the nature of the neurophysiological ERP responses recorded after the errors made by ADHD children (i.e. error-related negativity and positivity). Studied on different types of task, the negative response has been reported to be larger (Burgio-Murphy *et al.*, 2007), normal (Wiersema *et al.*, 2005) or reduced (Van Meel *et al.*, 2007). However, a participation of both DA and 5-HT projections in the neurophysiological response to an error of commission is evident in apparently healthy subjects. Here, the presence of one or two copies of the low-activity, short SERT promoter allele is associated with larger negative and positive ERPs following an error (Fallgatter *et al.*, 2005). The early negative ERP response also becomes larger in subjects treated with amphetamine (De Bruijn *et al.*, 2004).

This section has indicated that while DA and 5-HT interact in some of the endogenous mechanisms involved in selecting information for further processing, the best defined of these incur executive attentional control, where poor function results in cognitive impulsivity and variability.

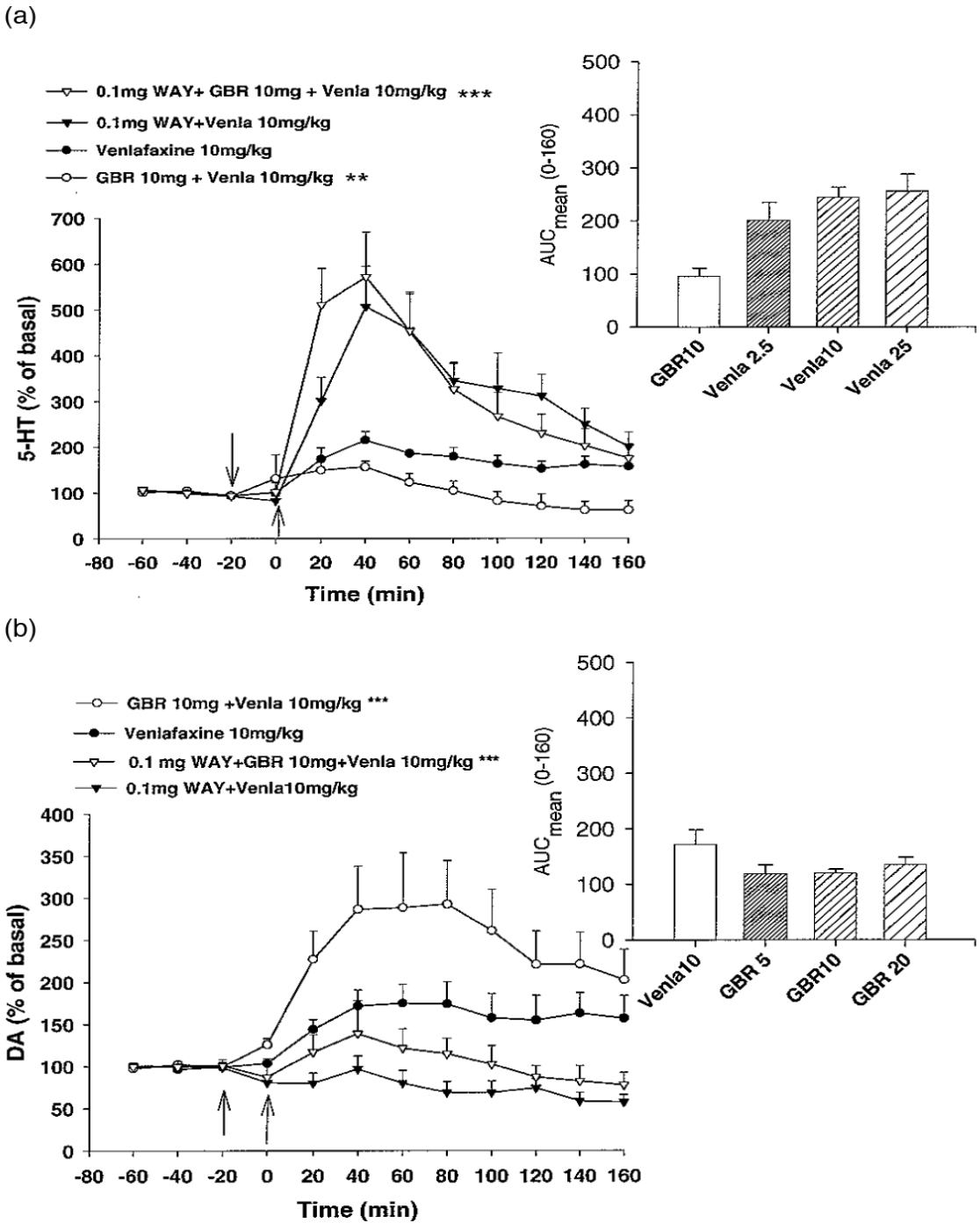
3.3 Studies of Medication show signs of interactions in ADHD

Given that that the efficacy of catecholamine reuptake blockade in ADHD is well established (section 2), it is appropriate to consider evidence about medication that affects the 5-HT system. There is considerable anecdotal experience suggesting that venlafaxine, an inhibitor at SERT and to a lesser degree the NA transporter (Gould *et al.*, 2006), can present an effective treatment, especially with adult patients with ADHD (Hedges *et al.*, 1995; Findling *et al.*, 1996; Popper, 2000). Open trials report a response rate of 50-78% that is comparable with psychostimulants (Findling *et al.*, 2007; Maidment, 2003). The primary reason for its use is reflected in its antidepressant profile. But as noted above, while lability of mood and affect is often a feature of ADHD, so also is the variability of behavior in a wider context. Indeed, the control by 5-HT activity of impulsive responses, whether of a cognitive or aggressive nature, represents a potential target for pharmacotherapy, albeit reflecting a need for alterations in different directions. Past experience with desipramine (inhibitor of NA and 5-HT uptake: Maidment 2003) and tranylcypromine (two enantiomers involved in inhibition of MAO and inter-ference with monoamine uptake (Baker *et al.*, 1991) is also relevant even though their prescription is now restricted due to the adverse side effects.

Evidence pointing to the relevance of 5-HT/DA interactions comes from pharmacological and neurobiological studies. Weikop and colleagues

Figure 4:

(a) Frontal 5-HT levels after venlafaxine alone (10 mg/kg, ip at 0 min) or with GBR12909 (10 mg/kg, sc at -20 min), or WAY-100635 (0.1 mg/kg, sc at -20 min) or all 3 substances. The inset shows the effects of 3 doses of venlafaxine co-administered with GBR12909 with respect to the area under the curve (0-160 min) for controls. **(b)** Frontal DA levels after the same 4 treatment as (a). The inset shows the effects of 3 doses of GBR12909 co-administered with venlafaxine (Modified after Weikop et al., 2007a and reproduced with the permission of Sage Publishers)



(Weikop *et al.*, 2007a, b) reported initially surprising results from microdialysis experiments using the frontal cortex of rats following combinations of treatments with agents that block reuptake. Adjunctive treatment of the specific 5-HT reuptake inhibitor citalopram with methylphenidate resulted in a large increase of DA over that recorded following methylphenidate treatment alone, but a marked reduction of 5-HT release compared to treatment with citalopram alone. These effects were not evident in the nigrostriatal system. The authors suggested that the effect on DA could reflect a local elevation of 5-HT tone resulting in disinhibition in the ventral tegmental area. Normally, such an autoreceptor (or presynaptic) effect might be expected to stimulate 5-HT_{1A} receptors that would increase DA release, and increase burst firing in the mesolimbic and mesocortical projections (Millan *et al.,* 2007). With systemic administration of other 5-HT uptake inhibitors, post-synaptic effects of 5-HT_1 stimulation can be expected that would result in decreased DA neuronal activity (Di Mascio *et al.*, 1998). Weikop *et al.* (2007a) also reported on the effect of blocking DA reuptake (with GBR 12909) at the same time as treating their animals with systemic venlafaxine. GBR 12909 alone had no effect on mesocortical monoamine levels. However, venlafaxine alone can increase DA, NA and 5-HT levels by 136-256%, reminiscent of the effect of tranylcypromine, while inhibiting firing in the dorsal raphe and locus ceruleus (Haddjeri *et al.*, 2004). The combination (as above) raised DA levels and reduced 5-HT levels further (figure 4). As noted above, the underlying mechanism could reflect postsynaptic activation of receptors in the 5-$HT_{1/3/7}$ families, blockade of the 5-HT_{2A} site and/or long-loop feedback to GABA neurons in the brain stem nuclei (Weikop *et al.* 2007a). Direct evidence is still required. Whichever way the studies are viewed, there is the strong implication that venlafaxine can influence DA/5-HT interactions in a way that can result in improvements in ADHD. There remain many questions of how this happens in detail.

It is noteworthy that a PET study of the effect of venlafaxine on brain glucose metabolism, which naturally focused on depressed patients, described marked decreases of metabolic activity in the orbito-frontal and medial frontal regions (Kennedy *et al.*, 2007). This is of interest, firstly because these regions overlap with those found in animal studies of DA and 5-HT activity changes in impulsive behavior on delayed reinforcement tasks (Winstanley *et al.,* 2006; section 3.2.3). Secondly, also on the topic of impulsive responses, the effect of tryptophan depletion in young healthy adults (Rubia *et al.,* 2004, see above) not only reduced activity in these frontal regions, but like the subjects of Kennedy and colleagues, increased right occipito-temporal activity.

Lastly, also on the subject of energy metabolism, it seems appropriate to mention one hypothetical locus for DA/5-HT interactions in ADHD that has received hardly any attention. Russell *et al.* (2006) proposed a re-direction of research effort to achieve a better understanding of the energy supply via the lactate shuttle from glia to neurons. They suggested that the variability of behavioral responsiveness in ADHD, previously mentioned in association with impulsivity, could be explained by a lack of energy from astrocyte sources to sustain rapid or burst firing in neurons when required. They also extended the hypothesis to account for delayed maturation and myelination in the CNS of those with ADHD (Shaw *et al.*, 2007) and attributed this to a lack of energy and precursor supply from the oligodendrocytes. To understand the relevance here it

is important to realize that most DA receptors have been localized on these glial cells [D1, D3, D4, D5: (Miyazaki *et al.*, 2004)]. Increased levels of catechol-amines, facilitated by methylphenidate treatment, stimulate glycolysis (Todd and Botteron, 2001). So what is the function of the 5-HT receptors also identified on astrocytes, namely 5-$HT_{1A, B, D, F}$; 5-$HT_{2A, B, C}$; 5-HT_6 and 5-HT_7 (Hirst *et al.*, 1998; Doherty and Pickel, 2001)?

The question of the nature of the function of monoaminergic binding sites on glia has hardly been tackled. However, it is not surprising that initial results suggest that the activation of 5-HT_{1A} sites in the amygdala and prefrontal regions can tone down the release of lactate stimulated by an environmental stressor (Uehara *et al.*, 2006). This was demonstrated by blockade of the effects of tandospirone with a specific 5-HT_{1A} antagonist. However, as the antagonist did not interfere with the similar effects of perospirone, it is possible that the affinity of this drug for 5-HT_{2A} and D2 sites may have come into play and also modulated the supply of energy. Also relevant in the context of this section, are the effects reported to follow treatment of an astroglia-microglia culture with venlafaxine (Vollmar *et al.*, 2007). They found that after provoking an inflammatory situation, venlafaxine promoted an augmentation of anti-inflammatory cytokines (TGF-β) and reduced levels of the pro-inflammatory cytokines (IL-6 and IFN-γ). Thus, it would seem likely that venlafaxine exerted anti-inflammatory effects that could have been due to the increased levels of monoamines that the treatment induced. The potential significance for ADHD is that a predominance of the pro-inflammatory cytokines would otherwise bias the metabolism of tryptophan towards neurotoxic metabolites such as quinolinic acid (Myint *et al.*, 2007).

In this section the idea has been put forward that combining pharmacological treatments that influence both the DA and 5-HT systems may have differential even opposite effects on the release and availability of these two monoamines, and that this can be associated with beneficial consequence for ADHD pathology. However, there is still a need for controlled studies of this claim. A further challenge requiring detailed study is to find out whether the purported consequences of DA and 5-HT uptake blockade result primarily from neuronal neurophysiology and/or glial energetics.

4. Discussion and Conclusions

For a consideration of 5-HT/DA interactions and their putative dysfunction in ADHD there are 3 major CNS territories of interest, the mesostriatal, the mesolimbic and the mesocortical. In the mesostriatal (and meso-thalamic) domain there are two features of special neurobiological interest relating to the nature of DA/5-HT interactions. Compared to the other DA projection systems, this is where the distribution of the DA transporter predominates. This is also where the 5-HT innervation primarily derives from the dorsal raphe. The anatomical nature of this input differs from that deriving from the median raphe in that it is construed to be better at volume control than at advancing specific synaptic control of the target regions (Vertes, 1991; Michelsen *et al.*, 2007).

The mesostriatal/thalamic mode of action contrasts with the situation in mesocortical projection regions. Here, extracellular DA availability is more under the control of synaptic COMT, and the release of 5-HT, mostly of median raphe origin, is more localized with the aid of clusters of boutons around the target neurons (Michelsen et al., 2007). The characteristics of mesolimbic structures lie between these two extremes, with the

innervation of specific parts of the hippocampus or amygdala arising predominantly from one or the other raphe complex (Steinbusch, 2008). The generalizations proposed here must be tempered by an awareness of a considerable overlap of these two modes of innervation. For example, far more 5-HT of dorsal raphe origin is released in the frontal than in posterior cortices: there is an inverse trend for 5-HT with origin in the median raphe.

One of the more salient difficulties in focusing on the contribution of 5HT/DA interactions in ADHD is the evident contribution of components of 5-HT controlled processes to the expression of frequently comorbid conditions such as conduct disorder (and its associated externalizing, aggressive characteristics). Short variants of the SERT promoter are associated with lower levels of SERT expression and high levels of extrasynaptic 5-HT. These features have been reported to have some association with signs of aggression and conduct disorder in young males (Beitchman *et al.*, 2006; Cadoret *et al.*, 2003) but also, infrequently, with ADHD (Cadoret *et al.,* 2003, Li *et al.* 2007). In view of the unequivocal association of ADHD and features of the DA system, one might speculate that a search for genetic associations between aspects of both monoamines and young people diagnosed with ADHD versus conduct disorder would help disentangle the relative contributions of these two monoamines. Perhaps the tagging of function to the COMT gene is an example. For example, COMT deficient mice, if male, are aggressive, rather as in humans (Gogos *et al.*, 1998): this forms a parallel to the association of the *met* allele in Chinese ADHD patients, if male (Qian *et al.*, 2003).

This review describes evidence for a role for receptors belonging to the 5-HT_1 and 5-HT_2 families of receptors in the interaction between the 5-HT and DA projection systems, and in some of the dysfunctions evident in ADHD. Descriptions of clearly too much or too little activity are often difficult to elucidate where it remains uncertain whether post- or pre-synaptic activity predominates, or an inhibitory interneuron permits disinhibition in the control of specific functions. Each is possible in the context of the expression of ADHD in an individual on the one hand, as comorbid with conduct disorder or, in another individual as being of the inattentive type. This has been illustrated by the contrast of behavioral versus cognitive impulsivity. More detailed neurobiological studies are necessary. Nonetheless, an understanding of the basic anatomical features (above) does provide a basis for prediction and further detailed investigation. For example, immunocytochemical work shows that more 5-HT_{1A} labeled dendrites in the ventral tegmental area are found in the nucleus parabrachialis than the nucleus paranigralis (Doherty and Pickel, 2001). This suggests that 5-HT_{1A} stimulation is more likely to influence mesocortical than subcortical DA function. Indeed, stimulation of these sites can have anomalous influences on DA function and executive attentional processes, such as those impaired in ADHD.

Until recently clinicians have seen little need to improve on the catecholaminergic model for explaining the features of ADHD. Recent genetic and neuroimaging studies, however, provide evidence for separate contributions of altered DA and 5-HT function in this disorder. Genetic studies imply that for both DA and 5-HT systems variants may frequently occur in ADHD for neurotransmitter uptake (DAT1, SERT), synthesis (TPH2, DDC) and breakdown functions (MAO and perhaps COMT). The mesolimbic (striatal) distribution of DAT1 and the mesocortical abundance of D4 binding sites, both

strongly implicated in ADHD, draw attention to the possibility of differential contributions from the 5-HT system. Here the evidence points not so much to region specific anomalies as a differentiation in terms of inhibitory/facilitatory pre/ postsynaptic location of receptors in the 5-HT_1 and 5-HT_2 families. Whether these receptor-based changes are secondary to the processes controlling transmitter availability is a question that remains to be answered. While levels of activity and metabolism (HVA and 5-HIAA) are often correlated, this may well flow from a starting point where 5-HT activity is anomalously higher or lower than the generally lower than normal levels for DA. It appears that perhaps both situations may arise reflecting different subgroups of ADHD, and where impulsive characteristics reflect externalizing behavior or cognitive impulsivity. This differentiation on a dimensional level however has yet to be studied systematically on the nosological level.

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