Dopaminergic enhancement of cognitive function

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Dopaminergic Enhancement of Cognitive Function

Mitul A. Mehta^{a,b,*} and Wim J. Riedel^{c,d,e}

^aCentre for Neuroimaging Sciences, Institute of Psychiatry, King's College, London, UK, ^bPET Psychiatry Group, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College, London, UK, ^cGlaxoSmithKline, Clinical Pharmacology & Discovery Medicine, Cambridge UK, ^dDept. of Neurocognition, Faculty of Psychology, University of Maastricht, NL and ^eDepartment of Psychiatry, University of Cambridge, UK

Abstract: The ascending dopamine system of the mammalian brain has been associated with motor, mnemonic and goal-directed or reward-related behaviour. The most progress in understanding the cortical mechanisms of dopaminergic modulation of function has been made with regards to short-term mnemonic (or working memory) function. Research in experimental animals strongly suggests that stimulation of dopamine D1 receptors in the prefrontal cortex can ameliorate spatial working memory related cognitive deficits, and may even enhance cognitive function in healthy animals. Research in humans has not been able to clearly replicate these findings, partly due to the lack of available agents that can safely be used. Low doses of dopamine D2 receptor agonists such as bromocriptine and pergolide may be able to enhance working memory and executive functions, but these effects may be dependent on the nature of the tasks used and the baseline performance levels of the subjects. Thus, the effects of dopaminergic cognitive enhancers may not be simple, or uniform across subjects. Systematic studies in humans carefully controlling task parameters are needed in order to specify the potential cognitive processes open to enhancement with dopaminergics. However, since the DA receptor subtypes in different brain regions appear to differentially influence similar functions, carefully defining the cognitive processes to be tested against potential therapeutics is an equally important goal. Studies in patients groups using selective dopaminergics are rather restricted, but show promise for designing large-scale clinical trials into the cognitive enhancing properties of potential therapeutic agents that act through the dopamine system.

INTRODUCTION

The ascending dopamine (DA) system of the mammalian brain has been associated with numerous functions. These include the regulation of motor output, reward-related behaviour, short-term memory and executive functions. While there has been considerable success in utilising the DA precursor levodopa¹, and DA agonists such as pergolide and bromocriptine in the treatment of motor dysfunction associated with Parkinson's disease, it is the prospect of cognitive enhancement that has driven much research into systems-level analyses of dopaminergic modulation in more recent years. The backbone of these efforts is formed by a considerable number of elegant studies carried out in experimental animals [4, 5]. Advances in human studies have been hampered by a lack of agents available to replicate the discrete manipulations performed in experimental animals, although some findings to date have suggested that the advent of such drugs could bring therapeutic benefits to a wide range of patients, including those with brain injury following trauma or stroke, schizophrenia, Parkinson's disease and attention-deficit hyperactivity disorder.

The purpose of the present article is to review the available evidence in human volunteers regarding the potential efficacy and prospects for dopaminergic enhancement of cognitive functions and the prospective application to various neurocognitive disorders. Studies in experimental animals have highlighted the particular importance of dopaminergic neurotransmission for accurate performance of tasks mediated by frontal lobe and basal ganglia regions, and consequently such tasks have also been the focus of research in humans. Therefore this review will be centred on cognitive functions mediated by these brain regions. Indeed, deficits in tasks sensitive to damage to the prefrontal cortex (PFC) and connected regions of the basal ganglia are impaired in all psychiatric disorders as well as in many patients with traumatic brain injury, Parkinsonian disorders and progressive cortical degeneration disorders. In order to provide context for the studies in humans an overview of key research in experimental animals will also be provided following an overview of basic dopamine anatomy.

DOPAMINERGIC PROJECTIONS AND DOPAMINE RECEPTORS

The ascending DA projections comprise 2 major systems supported by anatomical descriptions and recent molecular descriptions of global-gene expression diversity [6]. The nigrostriatal system projects predominantly from the substantia nigra pars compacta to the dorsal putamen and caudate nucleus (dorsal striatum) and globus pallidus. The ventral tegmental area (VTA) projects mainly to regions of the limbic system (e.g. nucleus accumbens, amygdala, anterior cingulate cortex) and widespread regions of the neocortex with

*Address correspondence to this author at the Centre for Neuroimaging Sciences (PO89), Institute of Psychiatry, London SE5 8AF, UK; Fax: +44 (0) 20 7919 2116; E-mail: m.mehta@iop.kcl.ac.uk

¹ Levodopa can also lead to increases in noradrenaline via neurons containing betahydroxylase, which converts DA to noradrenaline. However, changes in brain noradrenaline levels are considerably less than for DA, with some studies showing no changes [1-3].

higher density of projections to more anterior regions (meso-corticolimbic system) [7, 8]. Projections to posterior cortical regions and cerebellum are of considerably lower density. Receptor distributions show a similar pattern to the distribution of projection neurons, with the highest density of DA receptors in midbrain and striatal regions. Relatively high densities of receptors are also present in certain 'limbic' structures, including the amygdala and anterior cingulate cortex [9-11]. Cortical DA receptor densities are much lower with anterior brain regions having higher densities than more posterior cortical regions and the cerebellum. Indeed for these latter regions DA receptor densities are considered negligible in human and animal neuroimaging studies *in vivo* and are often used as 'reference' regions for defining receptor binding in other regions [12].

The structure and cellular functions of DA receptors have been reviewed extensively elsewhere [(e.g. ref. 13)] and therefore will only briefly be reviewed here. The physiological actions of DA are mediated by at least 5 distinct G-protein coupled receptor subtypes, termed D₁ – D₅ [14]. In 1978 two distinct subpopulations of DA receptors were first described, with one stimulating adenylate cyclase, and the other independent of this [15]. Kebabian and Calne [16] were the first to describe these subtypes as D₁ and D₂ receptors respectively. Subsequent studies have confirmed this distinction for both central and peripheral DA receptors ([see ref 17]). The D₅ receptor shows considerable homology with the DA D₁ receptor, so together they are referred to as D₁, or D₁-like receptors. The D₃ and D₄ receptors show considerable homology to D₂ receptors, so together they are referred to as D₂, or D₂-like receptors. Currently no compounds are licensed for use in humans that have significant selectivity for any one of the 5 receptor subtypes and therefore in this review we shall refer to the D₁ and D₂ receptor families, with specific mention of the D₁ – D₅ receptor subtypes only when appropriate.

DA is synthesized from tyrosine, which is derived from the essential amino acid phenylalanine, or provided from the diet. As illustrated in Fig. 1, tyrosine is catalyzed to DOPA by tyrosine hydroxylase in the rate-limiting step in the biosynthesis of the catecholamines DA and noradrenaline². DOPA is converted to DA by the enzyme L-aromatic amino acid decarboxylase. Synaptic DA is rapidly taken-up into the presynaptic terminal by the DA transporter or broken down by enzymes such as catechol-*o*-methyltransferase or monoamine oxidase. Fig. 1 also highlights the main mechanisms available for modulating central DA transmission, from alterations of precursor supply and blockade of transporter reuptake, to blockade of metabolising enzymes and direct action at the receptor sites. Although the use of some of these methods in the study of cognitive enhancement is limited (e.g. COMT-inhibitors such as tolcapone [19]), others (e.g. the DA D₂ receptor agonist bromocriptine) are more widely used in research. The focus of studies cited in this

review is, therefore, necessarily inclined towards the latter methodology, even though markers 1-5 in Fig. 1 should also be considered as potential targets for modulation of DA neurotransmission for cognitive enhancement.

Fig. (1). Representational organisation of a dopamine (DA) synapse with a presynaptic dopaminergic projection neuron shown above and postsynaptic neuron (e.g. GABA neuron in the striatum) shown below. Tyrosine (Tyr) is converted to DOPA by the enzyme tyrosine hydroxylase (TH), which is subsequently converted to DA (black dots) by L-aromatic amino acid decarboxylase (L-AAD). DA in vesicles exchanges with non-vesicular DA (nvDA). Extracellular DA is either rapidly taken up into the presynaptic terminal by the dopamine transporter (DAT) or metabolised by, for example, monoamine oxidase B, or catechol-*o*-methyltransferase (COMT). Synthesis and release modulating autoreceptors (4) may be distinct receptor sites. Numbers indicate possible mechanisms by which dopamine neurotransmission may be modulated. Depletion or supplementation of the dopamine precursor, Tyr, results in reduced or increased synthesis and release of dopamine (1). Levo-dopa administration can increase dopamine synthesis and release (2). Blockade of the DAT with stimulant drugs such as amphetamine, methylphenidate, or cocaine, results in increased extracellular DA levels (3). Psychomotor stimulant drugs such as amphetamine and cocaine can also stimulate release of vesicular DA stores (3). Dopamine receptor agonists and antagonists can directly influence presynaptic and postsynaptic DA receptors (4). Alterations in metabolism (5) have been shown to result from different genetic polymorphisms or direct modulation of enzymatic function (e.g. tolcapone is a brain penetrant COMT inhibitor). DA receptors are members of the seven transmembrane domain G-protein coupled receptors. DA D₁ receptors are coupled to G_s and stimulate adenylate cyclase, whereas DA D₂ receptors are coupled to G_i and inhibit adenylate cyclase. Co-expression of DA receptor subtypes is observed in a number of brain regions.

² However, it has been suggested that the synthesis of DA is not *solely* dependent on the availability of brain tyrosine levels. *In vitro* studies have shown that in a tyrosine-free medium DA synthesis continues, suggesting other sources of tyrosine can support DA synthesis. Among these are mobilised bound tyrosine, a low-molecular-weight peptide, like a dipeptide, or tyrosine from non-dopaminergic neurons [18].

EXPERIMENTAL ANIMALS

Dopaminergic manipulations in experimental animals have demonstrated numerous functions associated with distinct brain regions that are dependent on intact DA transmission. For example, dopaminergic projections to the PFC and striatum are involved in spatial working memory functions, and striatal and amygdala DA are important for learning/conditioning. This review will focus on frontal and striatal regions as the most progress has been made for functions predominantly mediated by them in translating research in experimental animals to humans.

The delayed-response task was one of the first cognitive tests shown to be sensitive to damage to the PFC. Ablation, excitotoxic damage, or cooling of the region around the principal sulcus in the lateral PFC of the monkey impairs accuracy of memory-guided performance on this task of spatial working memory without impairing stimulus-guided motor responses [20-25]. In this task and its variants the animal is required to view a stimulus in a specific location before a short delay (typically a few seconds, although DA may also be important for memory over much longer delays [26]). After the delay period the animal is required to make a correct memory-guided spatial response in order to receive a reward. In a landmark study Brozoski and colleagues [27] showed that after 6-hydroxydopamine (6-OHDA) lesions of the PFC in 3 monkeys, performance on a version of the delayed-response task was impaired to a similar extent as surgical ablation of the same area (later replicated by Roberts and colleagues [28]). Despite the fact that the pharmacological lesions also depleted noradrenaline and serotonin, but to a lesser extent, the authors concluded that DA was the neurotransmitter responsible for the impairments based on 2 additional findings. First, other animals with more significant noradrenaline and serotonin depletion, but less DA depletion showed no evidence of impaired performance. Second, systemic administration of the DA precursor, levodopa or the non-selective DA agonist, apomorphine, reversed the impairment in the DA depleted animals. Although the delayed-response task as used by Brozoski and colleagues and others has been criticised because the animal can change its posture during the delay in accordance with the spatial location of the reward this appears to occur rarely. An oculomotor version of the delayed-response task (ODR) is free from this confound, and is also sensitive to dopaminergic manipulations within the PFC. Direct application of specific DA receptor agonists and antagonists can modulate accuracy of performance and associated neuronal activity during the delayed-response task. Direction selective neurons showing sustained activity during the delay period of delayed-response tasks, or 'memory fields', are modulated by DA D1 selective compounds, but not DA D2 selective compounds [29-31]. By examining the effects of iontophoretic application of the DA D1 selective antagonist SCH31966, Williams and Goldman-Rakic [30] showed that concentrations just above threshold for effect dramatically enhanced the memory fields of prefrontal cortical cells; this effect was reversed by a DA D1 receptor agonist. However, with higher doses of the same DA D1 receptor antagonist the memory fields were markedly disrupted. The relationship between DA D1 receptor stimulation and activity of memory fields was formulated as non-linear by this study and subsequent behavioural

investigations in both rodents and monkeys [30, 32-35]. Thus, the spatial tuning of prefrontal neurons engaged in spatial working memory is enhanced at moderate levels of D1 receptor stimulation and reduced at both lower and higher levels of stimulation. This specificity of action can be accounted for by the location of DA D1 receptors on the spines of pyramidal neurons, modulating excitatory output from the PFC, while controlling inhibitory neuronal modulation of the same output [36].

Impairments in spatial working memory induced by downregulation of DA D1 receptor function after chronic treatment with the non-selective DA antagonist haloperidol, or with ageing, can be reversed by systemic administration of the DA D1 receptor agonist prodrug ABT-431 [37, 38]. This drug is converted into a potent full agonist of the DA D1 receptor in the brain and early studies in Parkinson's disease suggest that it may be a useful agent to assess therapeutic enhancement of working memory in humans [39]. In younger monkeys with no DA depletion even a sensitizing regimen of low doses of ABT-431 failed to produce enhancements in spatial working memory clearly seen in older monkeys [37]. While the same may not be true in human volunteers, as studies using agonists with DA D1 receptor affinity can improve spatial working memory performance in younger subjects [40], these findings do accord with previous suggestions that healthy individuals may be performing close to their optimum level for working memory and therefore it may be easier to impair rather than enhance their performance [41, 42].

Older animals are also sensitive to the effects of DA D2 receptor agents in modulating spatial delayed-response performance. When given *systemically*, delayed-response performance is enhanced by moderate doses of the DA D2 receptor agonist quinpirole, but not lower doses (thought to act predominantly *via* presynaptic autoreceptors) [43]. In younger monkeys, without loss of DA D2 receptor function, lower doses of quinpirole impaired delayed-response performance, whereas moderate doses enhanced performance. Fine motor performance and "hallucinatory like" behaviours were also modulated by systemic administration of quinpirole. Taken together, the findings were interpreted as reflecting a greater loss of prefrontal rather than motor area DA function with age. However, since the study used systemic administration of quinpirole, action in the striatum to modulate delayed-response performance cannot be ruled out. Indeed 6-OHDA lesions of DA in the caudate nucleus can also significantly impair performance of marmoset monkeys on the delayed-response task [44].

In addition to accurate performance of the delayed-response task, DA cell firing in the VTA is also thought to be important for acquisition or learning of the task [45, 46]. These findings formed the basis of a more general theory developed by Schultz and colleagues [47, 48] that learning may be driven by errors in expectations of salient, or rewarding [49] events, with DA neurons signalling such errors. In a simple stimulus-reward association learning task DA neurons fire to unpredicted rewards or reward-predicting stimuli, but do not fire to predicted rewards, and are depressed by omitted rewards. DA may therefore act as an effective 'teaching' signal in learning cognitive tasks. The ini-

tial short-latency firing of DA neurons to unexpected stimuli has also been proposed to represent an essential component in switching attention to behaviourally important, salient stimuli [50], including apparently non-rewarding stimuli such as tones or lights. More recent accounts have, however, proposed that aversive stimuli (which are both salient and non-rewarding) may actually inhibit DA neuron firing and subsequently activate DA neurons through an opponent process [49]. Resolution of these differing views may have implications for understanding the precise effects of DA agents in modulating various forms of learning.

In addition to attentional switching discussed above, other aspects of attentional function may also be modulated by, for example, administration of specific DA receptor agents to the medial PFC in the rat [51]. Performance of a continuous performance test requiring sustained and divided attention to spatial cues was unaffected by DA D2 receptor agents. The effects of DA D1 receptor drugs, was, however more complicated. Animals performing well at baseline, before drug administration (>75%), were impaired in terms of performance accuracy by the DA D1 antagonist SCH23390. For animals with poorer baseline performance (<75%), medial PFC infusion of the D1 DA receptor agonist SKF 38393 improved accuracy. Although the precise neuronal mechanisms underlying these performance changes have not been elucidated to the same level as those described for spatial working memory, these results strongly suggest that, as with working memory functions, there is an optimal level of DA D1 receptor stimulation required for accurate attentional performance. Importantly, they indicate that the effects of DA agents as potential cognitive enhancers may not be simple or uniform across groups of subjects. Indeed, preliminary results from some studies in humans support this conclusion [52, 53].

In conclusion, the research in experimental animals has shown that under-, or over-stimulation of prefrontal DA D1 receptors is associated with poor spatial working memory accuracy and, possibly, attentional performance. Although DA D2 receptors agents do not influence the activity of 'memory fields' in the PFC they may have a preferential role in prefrontal neural activity associated with memory-guided responding in the delayed-response task [54]. Moreover, the effects of specific DA receptor agents on subcortical activity related to working memory performance is yet to be described, but may be important in understanding the effects of *systemic* administration of compounds [42]. Striatal DA function (including the nucleus accumbens) is, however, important in learning and certain attentional functions [44, 55-57]. The lack of availability of selective ligands has also limited research into the precise role of other DA receptor systems such as DA D₃ or DA D₄.

STUDIES IN HUMANS

Lueck and colleagues [58] showed that patients with Parkinson's disease were impaired on an oculomotor version of the delayed-response task, demonstrating relevance of the studies in experimental animals to humans. However, since the patients were medicated with dopaminergics at the time of investigation it is difficult to determine the precise role of DA in the impairments seen. Indeed, despite impaired per-

formance in patients when compared to controls [59], studies of the effects of dopaminergic medication on this task show no clear performance changes in patients [60, 61] (spatial working memory tasks that require additional strategic, or executive functions may, however, be sensitive to dopaminergic medication in Parkinson's disease [60, 62]). In healthy volunteers, bromocriptine, a DA D2 receptor agonist, was shown to improve delayed-response performance accuracy in 8 adults [63] using a dose of 2.5mg. The task involved pointing to a spatial location presented on a computer screen 8 seconds earlier. Unfortunately, the improvement of 44% in spatial accuracy of recall was not replicated in a larger group of volunteers [64]. This same study did however show improved spatial recall accuracy with a lower dose of bromocriptine of 1.25mg. It was suggested that a higher incidence of mild side effects (e.g. nausea) experienced by the group given 2.5mg bromocriptine may have 'masked' any improvement in performance, or that the differences in timing of task administration relative to drug ingestion may explain differences between studies. The non-selective DA antagonist haloperidol produced impaired performance on the spatial working memory task in the same study, while a non-spatial analogue was unaffected by either drug. This was taken as evidence that DA manipulations may be more effective in modulating spatial rather than non-spatial working memory, a notion supported by a more recent investigation using both bromocriptine (2.5mg) and pergolide (0.1mg) that was unable to show modulation of an object working memory task (the task battery did not include a spatial working memory task) [65]. Although the group that conducted the original investigation of bromocriptine and working memory also demonstrated improvement in spatial working memory after 1.25mg bromocriptine in a subsequent study [66], other groups were not able to demonstrate the same effects with 2.5mg bromocriptine [40, 52, 67]. A more complex task measuring spatial memory span was improved in one study using 1.25mg bromocriptine [68], although other spatial memory tests were unaffected.

The mixed findings of studies using bromocriptine with spatial working memory tests are summarised in Table 1 and collectively suggest that while performance may be improved, a lower dose of drug may be more effective. Since bromocriptine is a DA D2 receptor agonist, more reliable effects on spatial working memory performance may be seen after administering a drug that is more potent as an agonist at the DA D1 receptor as suggested by research in experimental animals. Pergolide (a mixed D1/D2 receptor agonist) at a dose of 0.1mg did improve spatial working memory performance in a group of 16 volunteers, but only at longer delays of 16 seconds, not 8 seconds [40]. (In the same study 2.5mg bromocriptine did not influence performance in a separate group of 16 volunteers.) The preferred conclusion of this study is that the additional effect of pergolide at DA D1 receptors is responsible for the improved performance seen. However, as has previously been noted [69], pergolide is significantly more potent an agonist of the DA D2 receptor than bromocriptine, and therefore it remains possible that the observed improvements in spatial memory were due to action at the DA D2 receptor. Although plasma prolactin levels were reduced by similar amounts by both drugs this hormonal marker of DA D2 receptor effects may not be sensitive to

Table 1. Spatial Working Memory Tasks and the Effects of DA Agonists on Performance in Healthy Volunteers

Drug reference	Agonist at D1/D2 receptor?	Improved performance in spatial delayed-response task (or similar)
Bromocriptine [63]	D2	✓
Bromocriptine [64]	D2	✓ ^a
Bromocriptine [66]	D2	✓
Bromocriptine [52]	D2	×
Bromocriptine [40]	D2	×
Bromocriptine [68]	D2	✓ (spatial span test) ^b
Bromocriptine [67]	D2	×
Pergolide [40]	D2/D1	✓ (spatial pattern recognition test)
Pergolide [72]	D2/D1	×
Pergolide [67]	D2/D1	×

^a Improved performance only seen with lower dose. ^b A spatial recognition task, and self-ordered spatial search task were unaffected by bromocriptine. ^c A subgroup of volunteers with the higher baseline memory span scores had improved accuracy after drug on the delayed-response task. A spatial span task was unaffected, but was also improved in the higher baseline memory span group.

differences in receptor stimulation at 'low' doses [70, 71]. Unfortunately, two more recent study using 0.1mg pergolide were both unable to clearly demonstrate improved spatial working memory performance using spatial and object variants of the delayed-response task [67, 72].

When baseline reading span was factored in to the analysis of the pergolide study by Kimberg and D'Esposito [72], the clearest finding was a relative improvement in delayed-response performance accuracy (spatial and object), but only in the group with a higher reading span. This result parallels earlier findings from the same group using 2.5mg bromocriptine for which performance on more 'executive function' tasks such as the Wisconsin Card Sorting Test was improved in high-span subjects, but worsened in low-span subjects [73]. However, both of these findings oppose the results of earlier studies [52, 53, 68], in which performance was improved in the low-span subjects. Kimberg and colleagues [52] did not observe main effects of bromocriptine on spatial delayed-response or executive function measures, but did observe interactions with baseline reading span for the executive function measures. Those with low reading spans (as determined by a median split) were improved and those with higher spans were worsened by bromocriptine. A number of differences exist between this and their later study [73] which showed the opposite effects, including subtle changes in task parameters, different numbers of participants, and a different delay between drug ingestion and neuropsychological assessment. The different delays are important because this could influence the magnitude and type of effect observed. For example, bromocriptine is thought to have biphasic effects, such that at low doses (or early in its pharmacokinetic timecourse, i.e. before t_{max} during absorption and distribution of the drug) it has predominantly pre-synaptic effects, whereas at higher doses (or later in its timecourse, i.e. after t_{max} during elimination of the drug) it has predominantly postsynaptic effects [74, 75].

Differences in task parameters across the studies described may also be responsible for the differential effects seen. For example, the studies by Luciana and colleagues showed improved delayed-response performance in a task that required memory-guided responses to spatial locations (see Table 1). Müller and colleagues failed to show improved performance on a task that required the recognition, rather than recall, of the location of complex pattern stimuli [40]. As noted by Luciana and colleagues [64], with regards to their own findings, such task differences may be described in terms of requirement for preparation of a motor response, rather than in terms of mnemonic function. The importance of the mesostriatal DA system in motor (response) readiness has previously been highlighted in both animal and human studies [76, 77]. However, it is difficult to ascertain the importance of the neuropsychological task parameters in the interpretation of the human studies as no systematic investigations have been conducted to date. Such a study would require the use of a series of similar tasks in which either the stimulus properties, or the nature of the delay period, or the mode of response (e.g. recall versus recognition) were varied. A recent study in Parkinson's disease used a similar design to examine the influence of dopaminergic medication withdrawal on manipulation versus maintenance of verbal information (sequences of 4 letters) held in working memory [62]. The results were clear. DA medication withdrawal led to worse performance when manipulation (reordering of letters) was required compared with maintenance. Similar studies have yet to be conducted in healthy volunteers.

The age of participants may also be an important factor due to possible 'naturalistic' reductions in markers of the DA system with age [78], and the more positive responses to DA agonist treatment seen in older animals [37, 43]. Indeed, some studies showed that improvement was greater in human volunteers with lower baseline ability (although others showed the opposite) [52, 53, 68, 72, 73]. There are, how-

ever, no clear examples of selective DA agonists being used with working memory and executive function tasks in elderly human volunteers. In one study [79], the DA precursor levodopa was shown to improve effortful memory, but not semantic memory in a group of elderly normal volunteers in a placebo controlled, double-blind study. Two other studies used the synthetic DA agonist piribedil. The first of these was conducted in a general practice setting with over 500 patients, most of whom showed improved memory, although the lack of a control group, or placebo arm makes interpretation of this study difficult [80]. The second study demonstrated improved acquisition of skill learning after 2 months of piribedil 50mg per day in 37 older volunteers, although the effect was limited to the group of volunteers aged 65-74, and was not present in those aged 75-82, suggesting variations in sensitivity to positive effects within older populations. In younger volunteers, a small placebo-controlled study by Schuck and colleagues [81] demonstrated improved immediate and delayed free recall after 3mg piribedil. A verbal working memory test based on the digit span test was also included in this study, but was not improved. Although piribedil acts directly on DA D2 and D3 receptors, as well as on D1 receptors *via* its main active metabolite, it is also an antagonist at α_2 -adrenoreceptors, suggesting that some of its apparent positive effects may be mediated, or even limited by its action on the adrenergic system. Thus, on the basis of these studies in humans and experimental animals, large-scale investigations of the memory enhancing properties of selective DA agonists are urgently required, particularly in older volunteers.

Even when studies are able to demonstrate a positive influence of dopaminergic intervention on cognitive function, not all participants respond. As already suggested, individual differences in baseline performance may be an important factor here. However, these and other putative differences that are yet to be described, could be mediated in part by genetic variations. These could influence numerous processes from pharmacokinetics [82] and enzymatic catabolism [83], to the binding of the drug at specific receptor sites [84]. Considerable interest has surrounded the identification of a substitution polymorphism of the catechol-*o*-methyltransferase (COMT) gene at codon 158 (COMT Val¹⁵⁸Met polymorphism) [83]. Broadly, the prevailing hypothesis is that the high activity form of COMT (the Val allele) leads to reductions in cortical DA levels and associated impairments in networks mediating working memory and other executive functions [85], although the COMT Val¹⁵⁸Met polymorphism could also affect other neurotransmitters - particularly noradrenaline - and other regions including the striatum [86], and the precise effects of such a polymorphism may also interact with disease processes [87]. Nonetheless, phenotypic variations due to such a genetic polymorphism could contribute to individual differences at baseline that predict drug response, or influence drug response directly [88].

In summary, the studies in healthy human volunteers to date have suggested that spatial working memory and other executive functions may be improved by administration of low doses of DA agonists. However, a number of prominent caveats are highlighted, including the nature of task design, the baseline ability and age of the subject, genetic polymor-

phisms and the relative potency of drugs at DA D1 and D2 receptors. It should also be noted that the repertoire of compounds used in these studies is limited, with no published studies using potent and selective DA D1 agonists available at the time of writing. In addition, most studies have been conducted in younger volunteers, whereas research in experimental animals has suggested that it may be easier to improve function in older subjects with 'naturally' impaired DA systems.

PSYCHOMOTOR STIMULANTS

Stimulant drugs such as amphetamine, methamphetamine, cocaine and methylphenidate can influence DA neurotransmission by blocking reuptake at the transporter site, thereby increasing extracellular levels of DA, and stimulating release from the presynaptic terminal. However, these compounds also have significant, but varying effects at the noradrenaline and serotonin transporter sites [89]. Therefore, attribution of possible cognitive enhancing properties of this class of compounds specifically to DA neurotransmission is problematic. Even so, the psychomotor stimulants do have a significant influence on the dopamine system and their widespread use in the treatment of ADHD, as well as their established ability to improve attentional function, even in healthy volunteers [90-92] indicate that they should not be omitted from a discussion of dopaminergic influences on cognitive function. Using the Cambridge Neuropsychological Test Automated Battery (CANTAB; www.cantab.com), Elliott and colleagues [93] demonstrated improvements on a number of tests sensitive to frontal lobe and striatal damage using 20mg and 40mg methylphenidate. A test of spatial working memory requiring ordered searches through an array of boxes for hidden tokens was improved, as was a test of sustained attention. The study also assessed planning ability on two versions of the Tower of London Test. In one version that required planning, but no execution of the plans, performance accuracy of the difficult problems was improved, but only on the first test session of the cross-over design. In another version that required execution of the plans subjects were less accurate, but quicker to initiate solution performance, for the difficult problems, but only on the second session of the cross-over design. These complex findings suggest that the effects of methylphenidate can interact with the novelty of the tests to the subjects, since they received no training sessions prior to the study. That is, the increased arousal associated with novelty, combined with administration of methylphenidate may act to improve performance, but the absence of novelty on the second session may disrupt performance, possibly *via* subcortical effects on DA systems. This evidence for this latter effect was the increased response times and impaired performance accuracy on the planning task.

Other studies using dopaminergic and noradrenergic agents have provided some support for interpretations of drug effects that incorporate novelty [94, 95]. However, in a follow-up study using the same spatial working memory test [53], 40mg methylphenidate was found to improve performance in 10 subjects that had received pre-study training. In a finding that paralleled earlier studies with bromocriptine [52], it was those with lower baseline memory spans that

showed the greater performance improvements after drug. The same 10 volunteers were also scanned using positron emission tomography during performance of the working memory task. This showed that methylphenidate modulated the dorsolateral PFC and posterior parietal lobe, suggesting that disorders affecting functioning of these brain regions may benefit from methylphenidate.

Rogers and colleagues [96] also tested the effects of 40mg methylphenidate on fronto-strially mediated cognitive function using a test of cognitive flexibility. A similar test had been used by Elliott and colleagues [93], but the drug did not influence performance. The test required the learning of stimulus-response associations to compound stimuli that could be segregated along two distinct dimensions. The key stage of the task required shifting attention from one dimension of stimuli to another, akin to a category shift in the Wisconsin Card Sorting Task [97]. The young healthy volunteers made very few errors and therefore we cannot be sure that a ceiling effect reduced the sensitivity of this task to possible effects of methylphenidate. By adding an extra dimension Rogers and colleagues [96] produced a version of the attention-set shifting task that was sensitive to methylphenidate, with the drug reducing errors during the key shifting stage, while responses were slowed. They concluded that increased catecholamine neurotransmission disrupted allocation of attention to relevant and irrelevant features of the environment. Children with ADHD given the attention-set shifting test in a similar study design showed remarkably similar effects on the same task, with methylphenidate reducing set shifting errors and thus, normalising performance [98].

In contrast to the findings in young healthy volunteers, and at odds with predictions from experimental animal studies described earlier, elderly male volunteers given a similar acute dose of methylphenidate (20mg or 40mg), showed no improvement on tests of self-ordered spatial working memory, digit memory span, spatial memory span, planning, attention-set shifting, or motor inhibition [99]. The authors suggested that the doses of methylphenidate used may have disrupted functioning of the PFC and that lower doses may still be effective for improving cognition in elderly volunteers. Alternatively, they suggested that the between-subjects design might have reduced statistical power to detect changes in cognitive performance. This explanation is in keeping with findings of baseline dependent effects of drugs, including methylphenidate, on cognitive function. A large variation in performance in the different groups may mask a small, baseline dependent effect of the drug.

In summary, methylphenidate is able to produce pronounced effects of spatial working memory and sustained attention in young healthy volunteers. The more complex findings on tests of planning and attentional-set shifting highlight that improvements in some areas of cognition may be accompanied by impairments in other areas. These effects have not been replicated in elderly volunteers, a group predicted to show enhanced effects of dopaminergic agonists from research in experimental animals, although we are yet to see within-subjects placebo-controlled studies examining this question in humans.

CLINICAL IMPLICATIONS

Persistent cognitive deficits are common complaints in a number of disorders including schizophrenia, attention deficit disorder as well as after traumatic brain injury and cerebrovascular accidents (CVA). Cognitive deficits can be a major hindrance to normal social living and achievement in school or the workplace. Intervention strategies can potentially reduce significant disability and considerable healthcare costs. The frequency of working memory and attentional deficits in a wide range of patients and the known involvement of DA in working memory function described in this review indicates that DA therapeutics are an important strategy in the amelioration of deficits in such patients. Discussion of clinical implications is focussed on three indications in order to give an overview of issues and limitations within the literature. The reader is directed to other recent reviews for a more general coverage of this topic in relation to other disorders [100-103].

Schizophrenia is commonly associated with numerous cognitive deficits, most notably in the domains of working memory and episodic memory, as well as more general deficits in executive function as suggested by difficulties on tests of cognitive flexibility and sustained attention. Goldman-Rakic and colleagues have reviewed the putative role of DA D1 receptor stimulation in targeting the working memory deficits in patients with schizophrenia [36, 104] in relation to pathological substrates and animal research. *In vivo* studies in patients with specific pharmacological challenges are, however, lacking. The precise nature of DA dysfunction in the PFC of patients with schizophrenia is also unclear. Three studies to date have used PET neuroimaging to measure the density of DA D1 receptors in the PFC of neuroleptic naïve patients with schizophrenia: one study showed reduced ligand binding [105], one showed no change [106], and a third study showed increased ligand binding [107]. The former and latter of these studies also demonstrated a significant correlation between cognitive task performance measures and dorsolateral PFC receptor densities. The main difference between the three studies is that the latter utilised a different radiolabelled ligand to the former two. The binding of the DA D1 receptor antagonist SCH23390 was decreased, or unchanged in patients with schizophrenia [105, 106], whereas the binding of another D1 antagonist NNC-112 was increased [107]. However, *in vivo* binding of these ligands is differentially affected by DA depletion, with SCH23390 showing a paradoxical decrease in binding and NNC-112 being unaffected [108]. Decreased endogenous DA within a competition model would predict increased numbers of available receptors for binding of the ligand. If the differences between the studies reflects the different ligands used, then the increased binding of NNC-112 may reflect an increase in DA D1 receptor expression secondary to a DA deficit in the cortex [109]. Together with the increased stimulation of subcortical DA D2 receptors previously hypothesised and reported [110], this is consistent with the notion of two co-existing levels of DA dysfunction in schizophrenia. Drugs that increase prefrontal cortical DA D1 receptor stimulation to target cognitive dysfunction may therefore prove to be a valuable adjunct to current neuroleptic drugs for targeting positive symptoms of the disorder such as hallucinations and paranoid and delusional thinking.

Cognitive deficits associated with ADHD may also benefit from DA stimulation and improved performance is often achieved after psychomotor stimulant treatment [98, 111-113]. The precise nature of cognitive deficits seen in ADHD and a complete review of the role of stimulant treatment in cognitive enhancement in ADHD is beyond the scope of this review, and has recently been discussed elsewhere in detail (e.g. [114-119]). In summary, ADHD appears to be associated with a wide range of deficits in areas of motor inhibition, sustained attention, episodic memory and motor timing, although there is current debate over the reliability of some of these deficits and specificity of some of these deficits to ADHD. While stimulant treatments, such as methylphenidate, can enhance performance on some of these domains, what is currently lacking is studies attempting to parse out these improvements to changes in dopaminergic or noradrenergic neurotransmission [42, 116]. Non-selective DA agonists have been used in small samples of children. Piribedil and amantadine (a non-competitive NMDA antagonist that also results in DA release) were not found to be clinically effective [116]. This may have been because the doses used were too high. Levodopa was effective in a number of small studies (but with some suggestion of less efficacy than methylphenidate) [120, 121]. However, none of these studies examined the potential cognitive enhancing properties of dopaminergic agents in these hyperactive groups. Langer and colleagues [122] tested the effects of a 3-week titration of levodopa (with carbidopa to minimise peripheral metabolism) up to doses of 600mg per day in a placebo-controlled design in 8 hyperactive boys. Teacher ratings of hyperactivity were reduced after levodopa. Sustained attention performance was also improved, with accuracy improving with faster stimulus presentation. A verbal paired associates learning task previously shown to be sensitive to an acute dose of amphetamine [123] was unaffected by levodopa. A more recent study used the non-selective DA agonist, pergolide, and showed improved performance in tests of memory and learning in a group of 7 children with restless leg syndrome and ADHD [124], but did not include a control, or placebo group to compare with the drug treatment group. Such methodological problems diminish the current utility of this and other studies. Moreover, diagnostic criteria have altered since most of these studies were initially conducted, with criteria for study entry often poorly specified. Amongst the studies conducted none have investigated the effects of selective dopaminergic, or noradrenergic agents on tests of working memory, defined in animal research as highly sensitive to prefrontal cortical DA D1 receptor stimulation. The only study conducted to date that attempted to separate dopaminergic and noradrenergic effects on cognitive function used a within-subjects randomised design to compare the effects of an acute dose of methylphenidate, levodopa and desipramine (noradrenaline reuptake inhibitor) on attention and inhibition in 16 boys with ADHD. Methylphenidate improved performance accuracy and reduced reaction times on a go- no go task, whereas levodopa and desipramine had no effect. In contrast, performance on a stop-signal reaction time task was only improved after desipramine. Thus, the authors concluded that while no ameliorating effects of levodopa were noted, desipramine did not mimic the effects of methylphenidate and therefore neither a 'pure' dopaminergic nor noradrenergic

explanation is sufficient in understanding the effects of methylphenidate on inhibitory function [125].

The availability of effective pharmacotherapeutics for ADHD in the form of psychomotor stimulant drugs, may explain the rather restricted range of studies examining the effectiveness of selective DA agonists on cognition, in particular working memory in this disorder. A similarly narrow literature is available in patients who have suffered from Traumatic Brain Injury (TBI) or Cerebrovascular Accidents (CVAs). This is surprising considering that working memory and associated deficits are considered a core component of the cognitive deficits associated with TBI [126], with more recent evidence of spatial working memory deficits in patients with parietal neglect following infarction [127-129]. Indeed, there is considerable evidence for monoaminergic dysfunction following TBI, with circulating levels of DA and noradrenaline as possible markers of injury severity and functional recovery [130].

In a small study levodopa (combined with carbidopa) was given to 12 patients following TBI without a placebo control. Outcome measures were based on clinical observation, rather than more objective neuropsychological assessment, but suggested improvements in memory, attention and impulse control as well as cooperation and insight [131]. The time between injury and treatment ranged from 3-52 months in this study, and the observed improvements were dependent upon this interval. Cognitive improvements dependent on the post-injury period were also found in another uncontrolled study using multiple baseline assessments (A-A-B-A design in which A=non-drug and B=drug) and methylphenidate with 11 patients [132]. Significant improvements in attention were demonstrated for those tested 4-71 days post-injury. In a placebo-controlled study using 2.5mg bromocriptine, McDowell and colleagues [133] demonstrated improved performance in tasks of executive function (including the Stroop test, verbal fluency and a dual-task paradigm), but not spatial working memory in a group of patients with TBI. Unfortunately, the authors did not report if these improvements were related to the length of post-injury period, which ranged from 27 days to 25 years. Another limitation of their study is that they only examined the effect of a single dose. Therefore, the precise role of post-injury time in dopaminergic enhancement of cognitive recovery is unknown, and requires further exploration as one potentially important predictor of treatment response.

In a more recent study (only published as an abstract) [134], bromocriptine has been shown to have differential effects in healthy controls and patients studied, shortly after mild TBI, on verbal working memory performance and associated changes in brain activation measured with functional magnetic resonance imaging (fMRI). Following bromocriptine, the healthy controls showed improved working memory performance and greater anterior frontal brain activation, whereas the patients showed a decline in performance and greater posterior frontal and parietal activation, suggesting altered mechanisms of action of a DA D2 receptor agonist, at a systems-level, in the patients.

In addition to potential enhancements of working memory and attentional performance, DA agonists may also be beneficial in improving motivational function, assist in re-

covery from aphasia and have neurotrophic/neuroprotective effects. Powell and colleagues [135] describe a study in which bromocriptine was administered to 11 TBI patients. Following multiple baseline assessments, the authors reported improved motivational and cognitive functions in the absence of mood changes. In 8 of the 11 patients these improvements remained after bromocriptine withdrawal. Since all patients in this study received bromocriptine it is not known if the effects are greater than the effects of placebo, or no treatment. Passler and colleagues [136] also used bromocriptine (2.5mg, given as 2 x 1.25mg) in an uncontrolled study with 5 patients with TBI who fulfilled the criteria of vegetative status (TBI-VS). The authors note that these patients recovered faster than a comparable group of cases described in the literature. The outcome measures were the Disability Rating Scale and the Coma Recovery Scale. Notwithstanding the difficulties in conducting studies in such patient groups, from a methodological point of view this investigation does not fulfil the basic characteristics of a scientific study. Therefore, we cannot be confident in the conclusions about bromocriptine. Furthermore, there is no unanimity about the mechanism of action that could explain accelerated recovery. The described improvements in patients following TBI could be due to the specific agonist action of bromocriptine at DA D2 receptors. One mechanism mediating recovery could be direct stimulation of brain regions, modulating cognitive deficits associated with injury. However, as this review has demonstrated (e.g. Table 1) the evidence for this is currently lacking, and limited studies have been conducted in patients. Alternatively, this form of dopaminergic stimulation could lead to accelerated recovery after TBI or TBI-VS by neurogenesis (new formation of neurons and/or their outgrowth) of dopaminergic- and/or other neurons [136].

There have been some reports examining the potential for dopaminergics in the treatment of aphasia. Aphasia (currently used interchangeably with dysphasia) describes linguistic difficulties associated with a brain lesion, commonly following a CVA. The cortical localisation of brain damage resulting in aphasia is varied, with much debate about the precise role of specific regions [137, 138]. Published studies with the dopamine agonist bromocriptine have generally been negative [139-142] with some studies showing positive outcomes for amphetamine [143, 144]. However, in a systematic review for the Cochrane database [145], which only included randomised controlled trials, no positive effects of amphetamine or bromocriptine on the treatment of aphasia after stroke were found. Nevertheless, there is one study that was aimed directly at investigating the interaction of pharmacotherapy and cognitive rehabilitation [144]. Although, the study used amphetamine, and therefore the critical mechanism of action could be dopaminergic, noradrenergic, or both, it deserves mention because of its methodology. Twenty-one patients with aphasia following stroke were given amphetamine (10mg), or placebo, in a double-blind study, for 5 weeks, starting 16 to 45 days after the infarct. During the treatment period there were 10 1-hour sessions of speech and language exercises each of which commenced 10 minutes after the administration of medication. The outcome measure of language function was the Porch Index of Communicative Ability, which was scored before treatment, 1

week after treatment and 6 months after treatment. The analysis conducted corrected for baseline differences in severity and age, but not duration since infarct. One week after treatment both groups had improved, although the amphetamine group improved 54% more than the placebo group. This reduced to 47% six months after treatment, but this difference was no longer statistically significant. Regrettably, the group sizes in this otherwise well-designed and interesting study were rather small (partly due to inclusion criterion of one CVA). The authors emphasised the importance of the hypothesis that pharmacotherapy is only useful when it is simultaneously combined with speech- and language therapy, as its therapeutic effect (i.e. plasticity) can be maximised under these conditions [144].

One of the main concerns in studying the effects of DA agonists, or psychomotor stimulants in recovery from TBI, or CVA in particular, is the significant risk of cardiovascular dysregulation. While not all of the aforementioned studies detailed the cardiovascular effects of the treatments used, when reported, no changes were observed [132, 144]. Importantly, a recent study in 40 healthy male volunteers showed that positive effects of acute amphetamine (0.25mg/kg) on novel word learning were independent of drug-induced increases in heart-rate, or blood-pressure [146]. Moreover, similar improvements were reported by the same group for levodopa (100mg for 5 days), which has a lower risk of cardiovascular dysregulation [147]. These studies have implications for the relatively safe reacquisition of sensorimotor and cognitive skills following brain injury.

In summary, the studies in clinical populations (illustrated here with schizophrenia, ADHD, TBI and CVA) suggest that dopaminergic agonists may be beneficial in the amelioration of some cognitive symptoms, although very few studies fulfil elementary criteria of evidence-based medicine. This means that in most cases an insufficient number of patients were included, a control condition (placebo) was lacking or double-blind administration was lacking. Another important issue is selection criteria. While justified in some cases, strict criteria can easily lead to difficulties in understanding how representative any findings are for the wider clinical population.

CONCLUSIONS

The weight of the evidence presented from research in experimental animals, human volunteers and patients suggests that increased DA stimulation may be beneficial for cognitive functions such as spatial working memory. While the animal research has placed a spotlight on DA D1 receptor stimulation on the apical dendrites of prefrontal pyramidal neurons, a role for DA D2 receptors, possibly in the striatum [148] as well as prefrontal cortical regions [54] cannot be discounted. However, there is a considerable degree of inconsistency in the evidence, particularly for humans (for example, Table 1). Stimulus properties (e.g. spatial vs. non-spatial stimuli), response style (e.g. recall vs. recognition), baseline performance level, genetic polymorphisms, task difficulty, dose of drug and acute versus chronic administration are prominent parameters that may prove to be important predictors of the cognitive effects of DA agonists. Systematic studies of these factors are yet to be conducted, but

are currently limited by safety concerns for dose ranges that can be safely administered to volunteers, together with the limited array of compounds that are available for use in humans. Alternative strategies, such as pharmacological 'subtraction' [40], or selective 'blocking' [149] designs may be employed to help delineate the effects of non-selective compounds on specific receptor systems. Such methods are, however, non-ideal due to difficulties in matching drug occupancy levels and potencies at receptor sites, as well introducing possible drug interaction effects.

In the published literature to date there has been a particular focus on spatial working memory processes and certain attentional processes, although findings from more recent studies have suggested a broader role for DA in influencing trial-and-error learning [48, 56], emotional memory [150, 151], emotional facial recognition [152], attentional switching [153, 154] and action monitoring [155]. The relative importance of DA receptor subtypes in these broader functions has also received less attention than for spatial working memory tasks and should be a focus for future studies. In addition there is predicted regional variation in these effects, with, for example, emotional memory modulation probably mediated in part by DA D₂ receptors in the amygdala [150].

Therefore, talking of 'DA function' *per se* may not be a useful strategy when considering the differential distribution of receptors across the brain and that selective ligands do not exist for each of the known subtypes of receptors (D₁ – D₅). For example, synaptic DA D₁ receptors in the PFC are known to be important for spatial working memory tasks in the monkey, whereas the distribution of DA D₅ receptors (which have affinity for DA a magnitude higher than DA D₁ receptors [156]) is distinct, possibly to facilitate diffuse dopamine reception [157]. Similarly the effects of altered DA neurotransmission in the striatum (including the nucleus accumbens) may be mediated *via* D₁, D₂, or D₃ receptor subtypes, with a particular challenge being the separation of effects at D₂ and D₃ receptor subtypes. While differential effects at these latter receptor subtypes is recognised as potentially important in understanding antipsychotic drug efficacies [158], the relative importance on cognitive function has received considerably less attention. Thus, a particular challenge for the future is a more refined understanding of the precise roles of DA receptor subtypes in mediating cognitive functions, with potential not only for cognitive enhancement, but also the prevention of context-specific cognitive impairment [159].

Such studies could benefit clinical investigations of dopamine agonists in the treatment of neurocognitive disorders. Although inconclusive, these have strongly suggested that DA neurotransmission is an important factor in improving cognitive impairments associated with certain disorders such as schizophrenia, attention-deficit hyperactivity disorder, Parkinson's disease and following head injury or a CVA. Moreover, studies of novel word learning suggest that DA agonists may accelerate recovery of language function, however carefully controlled studies in patients are necessary to confirm the potential utility of such interventions in clinical practice.

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