REVIEW

Translational Approaches to Frontostriatal Dysfunction in Attention-Deficit/Hyperactivity Disorder Using a Computerized Neuropsychological Battery

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent condition associated with cognitive dysfunction. The Cambridge Neuropsychological Test Automated Battery is a computerized set of tests that has been widely used in ADHD and in translation/back-translation. Following a survey of translational research relevant to ADHD in experimental animals, a comprehensive literature review was conducted of studies that had used core Cambridge Neuropsychological Test Automated Battery tests 1) to evaluate cognitive dysfunction in ADHD and 2) to evaluate effects of salient drugs in patients and in volunteers. Meta-analysis was conducted where four or more independent datasets were available. Meta-analysis revealed medium-large decrements in ADHD for response inhibition (d = .790, $p < .001$), working memory (d = .883, $p < .001$), executive planning (d = .491, $p < .001$), and a small decrement in attentional set shifting (d = .160, $p = .040$). Qualitative review of the literature showed some consistent patterns. In ADHD, methylphenidate improved working memory, modafinil improved planning, and methylphenidate, modafinil, and atomoxetine improved inhibition. Meta-analysis of modafinil healthy volunteer studies showed no effects on sustained attention or set shifting. Results were paralleled by findings in experimental animals on comparable tests, enabling further analysis of drug mechanisms. Substantial cognitive deficits are present in ADHD, which can be remediated somewhat with current medications and which can readily be modeled in experimental animals using back-translational methodology. The findings suggest overlapping but also distinct early cognitive effects of ADHD medications and have important implications for understanding the pathophysiology of ADHD and for future trials.

Key Words: ADHD, attention, CANTAB, dopamine, impulsivity, memory, noradrenaline, norepinephrine

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by symptoms of inattention, hyperactivity, and/or impulsivity (1). Attention-deficit/hyperactivity disorder symptoms interfere with scholastic, social, and workplace functioning and significantly impact upon quality of life. First described around 100 years ago as "hyperkinesis disorder of childhood," this clinical entity has evolved into DSM-IV ADHD, a disorder of considerable social and economic importance (2). The worldwide pooled prevalence of ADHD is 5% or greater (3). Attention-deficit/hyperactivity disorder is the most common psychiatric disorder occurring in children, and 30% to 60% of children with ADHD will go on to exhibit clinically significant symptoms into adulthood (4,5). The excess cost of ADHD, in terms of education, occupational impairment, and medical treatment, was estimated at $30 billion in the United States in 2000 (6).

Problems with cognitive function dependent upon frontostriatal circuitry are suggested by the core diagnostic criteria for ADHD and by experiences of patients. Impulsive, hyperactive, and inattentive symptoms hint at underlying dysregulation of impulse control and attention. Furthermore, patients often report difficulties with concentration, suppressing inappropriate behavior, planning activities in advance, and organization. Neuroimaging studies have identified brain abnormalities in patients with ADHD versus matched healthy control subjects, such as reduced volumes in the dorsolateral prefrontal cortex, caudate, and cerebellum (for reviews, see [2,7]). It is to be expected then that patients would exhibit dysfunction in cognitive domains dependent upon frontostriatal circuitry (8–11).

The objective and targeted assessment of cognition in ADHD permits exploration of the neural pathophysiology of this disorder, while assessment of the effects of ADHD-relevant pharmacotherapy aids in elucidating the mechanisms by which drugs exert their beneficial effects over psychiatric symptoms (12,13). Cognitive markers may prove useful in sample enrichment, in predicting treatment response, and in identifying novel therapeutic compounds for clinical trials (14). The aim of this article was therefore to evaluate cognitive dysfunction in ADHD and cognitive effects of drugs salient to ADHD in patients and in volunteers, as well as to survey the translational and back-translational potential through the use of comparable tests of cognition as enabled by the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery.

Evaluating Cognition Using CANTAB in ADHD: Translational and Back-Translational Aspects of the Neuropsychopharmacology

Many cognitive domains have been evaluated in patients with ADHD (e.g., [8–11,15,16–20]). However, there exist few testing batteries that have also been applied in back-translational and translational models to elucidate the salient substrates. One example of such a battery, which forms the focus of the present selective review, is the CANTAB (Table 1). The CANTAB has been widely used in academic studies with children from age 4 upwards through to old age (21–23).

Virtually all the cognitive tests described here have their counterparts in animal psychopharmacology, with the exception of the Tower of London (Stockings of Cambridge) test of planning (Table

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Table 1. CANTAB Tests Used in the Assessment of ADHD and Their Key Output Variables

	Domain and Associated CANTAB Test	Test Description (Approximate Time for Administration)	Key Measures
	Attention/Vigilance RVIP (24)	Continuous performance test of sustained attention. Participants monitor stream of single digits for a sequence of three-digit numbers (9 min).	Target sensitivity (A′), response bias (B″), commission and omission errors
	Working Memory SWM (25)	Self-ordered search task based on foraging behavior. Participants search array for tokens without returning to previous token locations. Measures include both efficiency and use of heuristic strategy (around 10 min).	Between-search errors, strategy scores
	Reasoning/Problem Solving IDED (26)	Test of cognitive flexibility, analogous to the Wisconsin Card Sort Test, with multiple stages segregating cognitive processes (around 10 min).	Errors to criterion at each task stage, especially extradimensional shifting
	Executive Planning SOC (27)	Visual planning task based on the Tower of London (28). Subjects must match a goal arrangement, either by moving balls around the screen (the classic version) or by working out the number of moves required "in mind" (around 8 min).	Mean attempts required to obtain correct solution, latency to respond
	Impulsivity SST (29)	Archetypal test of impulse control. Subjects made speeded button presses concordant with the direction of arrow stimuli. On a subset of trials, a stop-signal (auditory beep) occurs, signaling that the subject must inhibit their response (around 15 min).	SSRT, average reaction time on "go" trials

ADHD, attention-deficit/hyperactivity disorder; CANTAB, Cambridge Neuropsychological Test Automated Battery; IDED, intradimensional/extradimensional set shifting; RVIP, rapid visual information processing; SOC, Stockings of Cambridge; SSRT, stop-signal reaction time; SST, stop-signal task; SWM, spatial working memory.

2). This has enabled a good deal of translational neuropsychopharmacology in that 1) neural substrates of the animal tests can be matched with humans, to probe or substantiate possible homologies; and 2) the cross-species, comparative effects of drugs used to remediate ADHD can also be assessed. The fact that most of these drugs have their effects mediated by the monoaminergic systems greatly increases the chance of functionally homologous effects being defined, as there is considerable evidence that the main anatomical and functional aspects of these ascending neurotransmitter systems have been conserved in the mammalian brain.

Table 2. Comparable Tests for ADHD in Humans and Rodents

Human	Rodent
Continuous Performance, RVIP	5CSRTT, cross-modal sustained attention test (73)
Attentional Set Shifting, WCST	Intradimensional/extradimensional shift test
Self-Ordered Spatial Working Memory	Spatial delayed response, delayed alternation, delayed matching to position
Stop-Signal Reaction Time	Stop-signal reaction time

ADHD, attention-deficit/hyperactivity disorder; 5CSRTT, 5-choice serial reaction time task; RVIP, rapid visual information processing; WCST, Wisconsin Cart Sorting Test.

The 5-choice serial reaction time task (5CSRTT) for rodents was originally developed from a test developed for assessing effects of stressors and drugs on human performance (30). It is related to tests of continuous performance, including the rapid visual information processing (RVIP) task. Rats or mice are required to detect briefly presented visual stimuli randomly in space. Premature (impulsive) responses or errors of commission and omission are punished with time-out from positive reinforcement. Evidence of differential effects of selective and regional prefrontal lesions indicates that the rat uses virtually its entire prefrontal cortex to optimize aspects of performance on the task (31). The task has also been shown to be differentially sensitive to manipulations of the monoaminergic and cholinergic systems when tested with certain parameters. For example, D1 dopamine (DA) receptor agonists enhance discrimination of the targets when infused into the medial prefrontal cortex of rats (32); depletion of cortical noradrenaline produces significant deficits in discrimination under temporally unpredictable or distracting circumstances (33,34). Depletion of prefrontal acetylcholine by selective lesions of the basal forebrain also produce significant impairments in selective attention (35,36), a conclusion borne out by results

using a novel in vivo monitoring method for assessing cholinergic function and the effects of nicotine agonist drugs (37,38).

Early work found that poorly performing rats on the 5CSRTT showed behavioral enhancement when treated with low doses of methylphenidate (39). However, such improvements are not apparent when rats have been previously trained to a high level of performance, where methylphenidate can induce premature responding (e.g., [40]). Bizzarro *et al.* (41) found that if such impulsive responding was not punished, methylphenidate could be shown to produce improvements in discrimination performance. Work by Berridge *et al.* (42), using a different form of sustained attention task, has also shown beneficial effects of methylphenidate on performance in intact rats.

Atomoxetine does not produce increased impulsive (premature) responding on the 5CSRTT; rather, it tends to reduce such behavior, especially for rats with inherently high levels of premature responding (43–45). These effects occur at doses that have no impact on attentional accuracy on the 5CSRTT and thus are not due to sedative actions. Guanfacine has a similar, though less striking, effect to reduce impulsive responding (J.W. Dalley, personal communication). These data indicate a possible noradrenergically mediated response inhibitory process that may be related to that identified in human studies (46) and has been hypothesized on the basis of work with nonhuman primates (47–49). Intriguingly, under some conditions, for example, when rats are trained with variable intertrial intervals of stimulus presentation to reduce effects of expectancy, atomoxetine may even enhance the capacity to detect visual targets (E. Robinson, personal communication).

Studies of spatial working memory in nonhuman primates have revealed important modulation by both prefrontal dopamine and noradrenergic systems (for review, see [50]). Guanfacine has been found to improve aspects of working memory in monkeys (51,52), and in rodent studies the delayed alternation procedure has generally produced results that parallel those shown in nonhuman primates (47,48). In a very recent study conducted in monkeys, both methylphenidate and atomoxetine improved spatial working memory performance according to an inverted-U dose response (53). Furthermore, atomoxetine enhanced spatially tuned, delay-related prefrontal cortex (PFC) neuronal firing in monkeys at moderate doses but suppressed firing at higher doses. This enhancement was reversed by yohimbine, while the increased spatial tuning was reversed by a D1 antagonist.

For the intradimensional/extradimensional (IDED) task, there is a direct analogue of the human task for both rats and mice with corresponding demonstrations of the involvement of prefrontal cortical systems (54,55). Although, again, there has been little analysis of the effects of drugs such as methylphenidate, which has been reported to enhance extradimensional shifting in healthy human volunteers (56). Nevertheless, studies in nonhuman primates and rodents indicate a likely role for dopamine in the acquisition and shifting of attentional sets (57–59). Converging evidence in the rat also suggests a strong role for cortical noradrenaline in extradimensional shifting (60,61). This role is partly confirmed in work by Newman *et al.* (62) showing that low doses of atomoxetine enhance extradimensional shifting in rats depleted of cortical noradrenaline, although effects of methylphenidate were not tested. The animal literature is not yet conclusive on the relative role of dopamine and noradrenaline in set formation and extradimensional shifting (63). The evidence in marmoset monkeys is that dopamine is necessary for set formation ("stabilisation of representations" and unstable representations following PFC DA loss may lead to paradoxically improved set shifting in certain circumstances); whereas in rodents, noradrenaline has been shown via converging evidence to be necessary for extradimensional set shifting. However, as yet, there is no evidence concerning the role of noradrenaline on set shifting in monkeys and some data indicate a possible positive role for prefrontal cortex dopamine in extradimensional shifting in rodents. The reasons for this possible anomaly are discussed elsewhere (63) and may hinge around the use of bimodal sensory dimensions in the rodent IDED shifting paradigm, whereas the IDED tests in monkeys are all in the visual modality.

Finally, for the stop-signal reaction time (SSRT) (stop signal task [SST]) task, there is powerful evidence of comparable pharmacological effects in rats and humans. A viable SST task has been developed for rats, which, as for humans, appears to depend on cortical and striatal neural substrates (64–66). Importantly, the dissociable effects of atomoxetine and citalopram on the SST have been replicated in rats (45,67), enabling further studies to be undertaken on the neural basis of this enhancement of inhibitory control and its neurochemical basis. Bari *et al.* (67) also showed that the selective dopamine reuptake inhibitor GBR 12909 had no effect to improve SSRT, suggesting that atomoxetine's effects are not contingent upon enhancement of cortical dopamine. In fact, atomoxetine also increases the tolerance to delay in a temporal discounting task in which rats choose between small immediate rewards (one food pellet) and large delayed (e.g., by 20 sec) ones (45). Impulsivity on such temporal discounting tasks in children or adolescents with ADHD is also commonly observed, although performance on the SST and delayed discounting are often uncorrelated (68,69). These translational data suggest that atomoxetine can reduce different forms of impulsivity according to several measures, which may depend on distinct neural systems.

This demonstration of back-translation is important, not only in terms of validating the measures used in the animal tests, but also potentially in exploring the exact neurochemical and neural mechanisms underpinning therapeutic efficacy. Another excellent example is the drug modafinil, which, although it is not licensed in the treatment of ADHD, does produce a profile of effects consistent with possible benefits on inhibitory control (70,71). Again, use of comparable tests in rodents has begun to reveal the neurochemical mechanisms in ways that would be difficult to achieve in humans (72–78). A similar approach may be useful in characterizing agents with novel modes of action of potential use in ADHD, such as the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid positive allosteric modulators and novel nicotinic agonists (e.g., [38]).

Having considered translational aspects of the above paradigms, we now turn to a review of findings in humans, considering cognitive findings in ADHD versus control subjects, effects of ADHD-relevant pharmacotherapies in control subjects, and effects of ADHD-relevant pharmacotherapies in ADHD patients. For methods, see Supplement 1.

Neurocognitive Function in ADHD versus Healthy Control Subjects

The 13 available studies statistically comparing performance on the CANTAB tests of interest between ADHD and control subjects are summarized in Table 3. Two studies were not listed in the table as their primary intent was to assess drug effects and they did not statistically compare ADHD with control subjects (70,79); the earlier of these two studies was, however, included in meta-analysis, with the latter excluded as the reference control subjects were overlapping. There were sufficient data for meta-analysis of at least one key measure from every task, with the exception of rapid visual information processing, which was intact versus control subjects in the one available (adult) ADHD study (80).

Table 3. Studies Comparing CANTAB Performance in ADHD with Control Subjects

Citation	Sample Size Patients, Control Subjects (Age Patients)	Medication Status of Patients	Tests Used and Outcomes in ADHD Relative to Control Subjects				
			SST	SWM	RVIP	SOC	IDED
(81)	13, 13 (18–41 years)	3 on methylphenidate; withdrawn > 24 hours before testing	SSRT ↓ GoRT ↑ (trend) DE ↓				
(82)	48, 26 (6–12 years)	21 medicated/27 unmedicated		Strategy↔ Accuracy ↓ (unmedicated)			
(80)	20, 20 (adults)	11 medicated; withdrawn > 12 hours before testing	SSRT ↓ GoRT↔ Var GoRT↔	Strategy↔ Accuracy ↓	Accuracy↔		Accuracy↔
(83)	21, 21 (7–13 years)	All on methylphenidate; withdrawn 21–28 hours before testing	SSRT ↓ GoRT ↓ Var GoRT ↓				
(84)	19, 19 (19–39 years)	11 medicated; withdrawn > 24 hours before testing		Strategy ↓ Accuracy ↓			
(85)	279, 173 (11–17 years)	141 on methylphenidate; withdrawn > 24 hours before testing		Strategy ↓ Accuracy ↓		Accuracy ↓	SR ↓ Accuracy (EDS) ↓
(86)	53,53 (11–16 years)	32% on methylphenidate		Strategy↔ Accuracy ↓		Accuracy ↓	SR↔ Accuracy ↓
(87)	21, 32 (8–12 years)	≥ 14 medicated; withdrawn 48 hours before testing		Strategy↔ Accuracy ↓		Accuracy↔	SR↔ Accuracy↔
(88)	30, 15 (6–12 years)	15 medicated/15 unmedicated		Strategy↔ Accuracy ↓ (unmedicated)		Accuracy ↓	SR ↓ (unmedicated) Accuracy (IDR/EDS) ↓ (unmedicated)
(89)	19, 19 (19–39 years)	Where methylphenidate medicated, withdrawn > 24 hours before testing		Strategy ↓ Accuracy ↓		Accuracy ↓	SR↔ Accuracy (EDS) ↓
(90)[a]	75, 70 (7–15 years)	Medication naive				Accuracy ↓	SR ↓ Accuracy ↓
(91)[a]	75, 70 (7–15 years)	Medication naive		Strategy ↓ Accuracy ↓			
(92)	66, 26 (6–12 years)	26 medicated / 40 unmedicated		Strategy↔ Accuracy ↓ (unmedicated)			SR ↓ (unmedicated) Accuracy (IDR/EDS) ↓ (unmedicated)

Arrows denote difference in performance based on scores for the outcome measure stated: ↑, improved; ↓, impaired; ↔, no change.

Accuracy (RVIP: target detection; SOC: mean attempts to criterion, mean moves to criterion, number solved on first attempt; SWM: between search errors, within search errors, total errors; IDED: errors, trials to criterion); ADHD, attention-deficit/hyperactivity disorder; CANTAB, Cambridge Neuropsychological Test Automated Battery; DE, discrimination/direction errors; EDS, extra-dimensional shift; GoRT, mean/median reaction time for Go trials; IDED, intradimensional/extradimensional set shifting; IDR, intra-dimensional reversal; RVIP, rapid visual information processing; SOC, Stockings of Cambridge; SR, stage reached/stages completed; SSRT, stop-signal reaction time; SST, stop-signal task; Strategy, effectiveness of strategy employed; SWM, spatial working memory; Var GoRT, variability of reaction times for Go trials.

[a]Same sample under study.

Meta-analysis provided evidence for impairment in patients with ADHD across several domains. In terms of spatial working memory (SWM), patients exhibited large deficits in working memory (for graphic results of meta-analyses, see Supplement 1), making more total between-search errors (d = .883, $p < .001$) and exhibiting larger (i.e., worse) strategy scores (d = .507, $p < .001$). On SST, patients showed large deficits on the key measure of inhibitory control (d = .790, $p < .001$) but did not differ from control subjects in terms of median reaction times on "go" trials (d = .156, $p = .349$), suggesting a selective problem with inhibition. There was evidence for large executive planning deficits, such that patients solved fewer problems in the minimum possible number of moves on Stockings of Cambridge (SOC) (d = .491, $p < .001$). Cognitive flexibility, as indexed by IDED extradimensional shift errors, was impaired in patients overall but to a lesser degree (d = .160, $p = .040$).

Effects of Pharmacological Probes on CANTAB Test Performance

Healthy Volunteers

Studies using CANTAB tests to quantify effects of ADHD-relevant pharmacotherapy on cognition in healthy volunteers are summarized in Table 4 below. All studies used acute drug doses, and all were conducted in adults. Fourteen studies were identified in total, five using methylphenidate, five modafinil, two guanfacine, and two atomoxetine. These studies used a mix of parallel and crossover designs, and all were double-blind, placebo-controlled studies.

For modafinil (100–300 mg), there were five measures for which sufficient data were available for meta-analysis: RVIP A′, B″, and latency to respond; and IDED extradimensional shift errors and total errors. There was no evidence overall for significant effects of modafinil on these measures (most significant d = .209, $p = .237$).

Considering variables for which there were insufficient data for meta-analysis, findings with single doses of modafinil (100–300 mg) were inconsistent. Several studies identified beneficial effects of modafinil on aspects of executive planning, especially at harder levels of difficulty (SOC) (71,93); other studies did not (94–96), although two of these may have been limited by relatively small sample sizes ($n = 10$ and $n = 15$ per arm). One study found benefits on SSRT inhibitory control (71), while the other study, using a higher dose of modafinil (300 mg), did not (93). There was inconsistent evidence from single studies that modafinil worsened IDED performance (worsened in [95] vs. no effects in [71,94,96]) and improved target detection on RVIP (improved in [94] vs. no effect in [71,93,95,96]).

Of the methylphenidate studies (20–60 mg), one found overall significant beneficial effects of drug on SWM performance (97), while another found beneficial effects in the first testing session only (98). Another study, this time conducted in elderly adults, found no SWM benefits (99), possibly due to catecholamine depletion with advanced age. Clatworthy *et al.* (100) showed using positron emission tomography that where beneficial effects of methylphenidate on SWM did occur, these were significantly associated with drug-induced changes in raclopride binding in the striatum, thought to reflect dopamine release. This evidence for methylphenidate's mechanism shows some consistency with a functional imaging study in healthy volunteers, which suggested that methylphenidate (60 mg, used along with the dopamine antagonist sulpiride, 400 mg) can affect at least two different neural substrates: striatal (presumably via dopamine) and cortical (dopamine and/or noradrenaline), while influencing two distinct cognitive processes in probabilistic serial reversal learning: switching (striatal) and staying following reinforcement (dorsomedial prefrontal cortex) (101). In marmosets, PFC DA depletion does not affect reversal learning, suggesting that striatal DA is the important factor therein (102).

There was evidence that methylphenidate improved extradimensional shifting in one study (56), but this was not found in two others, including one middle and one older aged adult study (98,99). Methylphenidate also had no significant effect on attention/inhibition measures from RVIP in the two studies in middle and older aged adults, respectively (98,99). On SOC, the middle-aged adult study found that drug impaired or improved planning depending on session (98), while the study in older subjects found no overall effects (99).

Findings from the two studies assessing the effects of the alpha-2a receptor agonist guanfacine in healthy volunteers were mixed; one study found beneficial effects on SWM between-search errors and SOC executive planning (103), while the other found no significant effect on these tests but did identify a trend toward global slowing on the SST, suggestive of sedative effects (104). The drug doses of the two studies were likely to have been similar (dose 29 μg/kg, assuming mean weight 70 kg, ~2 mg in [103]; 2 mg in [104]).

For atomoxetine, a healthy volunteer study found beneficial effects of drug (60 mg) on the cardinal measure of impulse control, the SSRT (105). These findings were replicated in a subsequent functional magnetic resonance imaging study, this time using a 40 mg dose, and it was found that atomoxetine augmented right inferior frontal cortex activation (46).

Patients with ADHD

Studies examining the effects of pharmacotherapy on CANTAB tests in ADHD are summarized in Table 5. There were 10 studies in all, 9 crossover double-blind and 1 parallel double-blind. The majority of these were acute studies. Eight studies used methylphenidate, one atomoxetine, and one modafinil. In contrast to the healthy volunteer studies, for ADHD studies there was a mix of child/adolescent and adult trials in roughly equal measure. After accounting for studies that involved largely overlapping samples, there were insufficient data to meta-analyze single-dose effects of drug in these datasets. Findings from individual studies are therefore outlined below.

In the eight methylphenidate studies, a range of doses were used, some according to weight (.3–.5 mg/kg) and some absolute (5–20 mg). Methylphenidate improved aspects of SWM (between search errors) in two studies in children (106,107) and one in adults (79); however, no significant improvements were detected in another trial, published as two discrete articles using data from the same sample (91,108). Methylphenidate improved SSRT in both studies (one child, one adult) that included this task (81,83). In the one study using RVIP, methylphenidate improved target detection and shortened response latencies in adults (79). For SOC, the available trials detected no significant beneficial effects of methylphenidate (106–109). Methylphenidate was associated with IDED improvement in one of the child ADHD studies (more stages passed, especially in terms of extradimensional shifting) (107), while the other available study (reported as two articles, overlapping samples) in children with ADHD suggested no significant effects (108,109).

In the single available modafinil study (adults, dose 200 mg), treatment improved inhibition (lower SSRTs) and planning (fewer attempts to obtain correct solutions on SOC, with longer response latencies), with no significant effects on SWM or RVIP performance, with the exception that there was some evidence for benefits on RVIP for the first testing session only (70).

Table 4. Studies Examining Effects of ADHD Relevant Pharmacotherapy on CANTAB Tests in Healthy Control Subjects

Citation	Agent; Design	Sample Size (Group Age)	Tests Used and Outcomes on Treatment Relative to Placebo				
			SST	SWM	RVIP	SOC	IDED
(46)	Atomoxetine 40 mg; fMRI, acute, double-blind, placebo-controlled, crossover	19 (19–46 years)	SSRT ↑ (increased right inferior frontal activation) GoRT↔				
(105)	Atomoxetine 60 mg; acute, double-blind, placebo-controlled, parallel	60, 20 per arm (20–35 years)	SSRT ↑ GoRT↔				
(104)	Guanfacine 1/2 mg; acute, double-blind, placebo-controlled, parallel	60, 20 per arm (20–39 years)	GoRT ↓ (trend at 1 mg)	Strategy↔ Accuracy↔		Accuracy↔	Accuracy↔
(103)	Guanfacine 7/29 μg/kg; acute, double-blind, placebo-controlled, crossover	55, 6–12 per arm (23–35 years)		Strategy↔ Accuracy ↑ (29 μg/kg)		Accuracy ↑ (29 μg/kg)	Accuracy↔
(98)	Methylphenidate 20/40 mg; acute, double-blind, placebo-controlled, crossover	28 (adults)		Strategy↔ Accuracy ↑ (first session)	Accuracy↔ Latency ↑	Accuracy ↑ (first session) Accuracy ↓ (second session)	Accuracy↔
(99)	Methylphenidate 20/40 mg; acute, double-blind, placebo-controlled, parallel	60, 20 per arm (elderly adults)	SSRT↔ GoRT↔ DE↔	Accuracy↔ Strategy↔	Accuracy↔	Accuracy↔	Accuracy↔
(56)	Methylphenidate 40 mg; acute, double-blind, placebo-controlled, parallel	32, 16 per arm (adults)					SR↔ Accuracy (ED) ↑ (IDS) ↓
(97)	Methylphenidate 40 mg; PET, acute, double-blind, placebo-controlled, crossover	10 (adults)		Accuracy ↑ (with reductions in DLPFC and PPC blood flow)			
(100)	Methylphenidate 60 mg; PET, acute, double-blind, placebo-controlled, crossover	10 (22–32 years)		Accuracy↔ (improvement correlated with raclopride displacement in ventral striatum)			
(96)	Modafinil 100/200 mg; acute, double-blind, placebo-controlled, parallel	30, 10 per arm (19–23 years)			Accuracy↔	Accuracy↔	SR↔ Accuracy↔
(95)	Modafinil 100/200 mg; acute, double-blind, placebo-controlled, parallel	45, 15 per arm (50–67 years)			Accuracy↔	Accuracy↔	SR↔ Accuracy (total and ED) ↓ (200 mg)
(94)	Modafinil 100/200 mg; acute, double-blind, placebo-controlled, parallel	60, 20 per arm (19–22 years)		Strategy↔ Accuracy↔	Accuracy ↑ (200 mg)	Accuracy↔	SR↔ Accuracy↔
(71)	Modafinil 100/200 mg; acute, double-blind, placebo-controlled, parallel	60, 20 per arm (adults)	SSRT ↑ (200 mg) GoRT↔ DE ↑ (200 mg)	Strategy↔ Accuracy↔	Accuracy↔	Accuracy ↑	Accuracy↔
(93)	Modafinil 300 mg; acute, double-blind, placebo-controlled, crossover	12 (18–39 years)	SSRT ↔ GoRT↔		Accuracy↔	Accuracy ↑	

Arrows denote difference in performance based on scores for the outcome measure stated: ↑, improved; ↓, impaired; ↔, no change.

Accuracy (RVIP: target detection; SOC: mean attempts to criterion, mean moves to criterion, number solved on first attempt; SWM: between search errors, within search errors, total errors; IDED: errors, trials to criterion); ADHD, attention-deficit/hyperactivity disorder; CANTAB, Cambridge Neuropsychological Test Automated Battery; DE, discrimination/direction errors; DLPFC, dorsolateral prefrontal cortex; ED, extradimensional; fMRI, functional magnetic resonance imaging; GoRT, mean/median reaction time for Go trials; IDED, intradimensional/extradimensional set shifting; IDS, intra-dimensional shift; PET, positron emission tomography; PPC, posterior parietal cortex; RVIP, rapid visual information processing; SOC, Stockings of Cambridge; SR, stage reached/stages completed; SSRT, stop-signal reaction time; SST, stop-signal task; Strategy, effectiveness of strategy employed; SWM, spatial working memory; Var GoRT, variability of reaction times for Go trials.

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Table 5. Studies Examining Effects of Pharmacotherapy on CANTAB Tests in ADHD

Citation	Agent; Design	Sample Size (Group Age)	Tests Used and Outcomes on Treatment Relative to Placebo				
			SST	SWM	RVIP	SOC	IDED
(80)	Atomoxetine 60 mg; acute, double-blind, placebo-controlled, crossover	20 (adults)	SSRT ↑ GoRT↔ Var GoRT↔	Strategy↔ Accuracy↔	Accuracy↔		Accuracy↔
(108)[a]	Methylphenidate .3/.6 mg/kg BD; chronic 4-week, double-blind, placebo-controlled, crossover	75, 25 per arm (7–15 years)		Strategy↔ Accuracy↔		Accuracy↔	SR↔ Accuracy↔
(91)[a]	Methylphenidate .3/.6 mg/kg; acute and chronic 4-week (BD), double-blind, placebo-controlled, crossover	75 (7–15 years)		Strategy↔ Accuracy↔			
(109)[a]	Methylphenidate .3/.6 mg/kg; acute, double-blind, placebo-controlled, parallel	73, ~24 per arm (7–15 years)				Accuracy↔	SR↔ Accuracy↔
(107)	Methylphenidate .5 mg/kg (mean 18 mg); acute, placebo-controlled, double-blind, crossover	14 (9–13 years)		Strategy↔ Accuracy ↑		Accuracy ↓ (first session)	SR ↑ Accuracy (ED) ↑
(83)	Methylphenidate .5 mg/kg; acute double-blind, placebo-controlled, crossover	21 (7–13 years)	SSRT ↑ GoRT↔ Var GoRT ↑				
(81)	Methylphenidate 30 mg; acute, double-blind, placebo-controlled, crossover	13 (18–41 years)	SSRT ↑ GoRT↔ DE↔				
(79)	Methylphenidate 30 mg; acute, double-blind, placebo-controlled, crossover	18 (adults)		Strategy↔ Accuracy ↑	Accuracy ↑ Latency ↑		
(106)	Methylphenidate 5–20 mg; acute, double-blind, placebo-controlled, crossover	26 (6–12 years)		Strategy↔ Accuracy ↑		Accuracy↔	
(70)	Modafinil 200 mg; acute, double-blind, placebo-controlled, crossover	20 (adults)	SSRT ↑ GoRT↔ Var GoRT↔ DE↔	Strategy↔ Accuracy↔	Accuracy ↑ (first session)	Accuracy ↑	Accuracy↔

Arrows denote difference in performance based on scores for the outcome measure stated: ↑, improved; ↓, impaired; ↔, no change.

Accuracy (RVIP: target detection; SOC: mean attempts to criterion, mean moves to criterion, number solved on first attempt; SWM: between search errors, within search errors, total errors; IDED: errors, trials to criterion); ADHD, attention-deficit/hyperactivity disorder; BD, twice daily; CANTAB, Cambridge Neuropsychological Test Automated Battery; DE, discrimination/direction errors; ED, extradimensional; GoRT, mean/median reaction time for Go trials; IDED, intradimensional/extradimensional set shifting; RVIP, rapid visual information processing; SOC, Stockings of Cambridge; SR, stage reached/stages completed; SSRT, stop-signal reaction time; SST, stop-signal task; Strategy, effectiveness of strategy employed; SWM, spatial working memory; Var GoRT, variability of reaction times for Go trials.

[a]Same sample under study.

For the atomoxetine adult ADHD study, a single 60 mg dose was associated with beneficial effects of drug on SST (shorter SSRTs) and on RVIP (fewer errors of commission) but no significant effects on SWM or IDED performance (80).

Discussion

This article comprehensively reviewed ADHD studies and drug studies relevant to the disorder that had used the CANTAB, which is partly derived from tests used in studies of the neural and neurochemical basis of animal cognition. Examples of the utility of such cross-species translation are also surveyed. The validity of the battery in this respect is confirmed here by demonstrations of comparable effects following manipulations of homologous neural regions and of common effects of pharmacological agents often used in the treatment of ADHD.

The CANTAB was sensitive to cognitive dysfunction across multiple domains in ADHD, as confirmed by meta-analysis. We also found evidence that acute doses of medication improved aspects of cognition, though findings were more consistent in subjects with ADHD than in healthy volunteers. While the ultimate goal of remediating cognitive function in ADHD will depend on a drug's efficacy under chronic administration, the data indicate that beneficial effects on cognition can be quantified early in the treatment process. These effects on cognition may take time to translate into overt and measurable behavioral improvements in day-to-day life. It is also conceivable that some clinically relevant changes in cognition may require chronic dosing, perhaps reflecting downstream processes, e.g., changes in gene regulation, and synaptic structure/activity.

The identification of robust working memory impairments in ADHD (effect size .883, between-search errors) is consistent with previous work, including two meta-analyses that reported effect sizes of 1.06 and .63, respectively, using a variety of spatial working memory paradigms (18,110). A corpus of literature implicates dopamine in the modulation of aspects of spatial working memory (111–120), though it is important to assess whether noradenaline also plays a role. There was evidence that methylphenidate, which acts to increase dopamine by blocking reuptake and triggering release (74) (but which also enhances PFC noradrenaline function, perhaps to a greater degree, see [42]), improved working memory in middle-aged healthy adults but not in older subjects. Lack of effects in older subjects may reflect reductions in presynaptic dopamine levels with aging (121). In ADHD, beneficial effects of methylphenidate on

working memory were supported by data from the majority (three of four) of the available patient trials. These results are consistent with the notion that working memory and catecholamine (dopamine and noradrenaline) corticostriatal pathways are disrupted in patients with the disorder (97) and that these disruptions can be ameliorated by methylphenidate. There was no evidence from the available literature that modafinil significantly improved working memory or that atomoxetine improved working memory in adults with ADHD (single trial). The alpha-2a receptor agonist guanfacine improved working memory (and executive planning) in one healthy volunteer study but not in another. Beneficial effects of guanfacine on working memory have also been reported with a different working memory paradigm (122). Viewed collectively, and alongside translational data (53,123), results suggest a previously overlooked role for noradrenaline, as well as dopamine, in working memory and in the amelioration of working memory deficits by pharmacotherapeutic intervention in ADHD.

Problems with response inhibition are suggested by the impulsive symptoms of ADHD. We reported medium-large deficits in SSRT in ADHD versus control subjects in meta-analysis (effect size .790). Our results are consistent with other meta-analyses comparing ADHD with control subjects that reported effect size of .64 and .51 on commission errors during continuous performance tasks (10,110) and .58 and .61 for stop-signal reaction times (9,110). Response inhibition is dependent upon a distributed neural network, including the right inferior frontal gyrus, bilateral anterior cingulate cortices, and (pre-) supplementary motor area (124–126). Aspects of inhibitory control, including SSRT, have been improved in rodents by systemic dosing with methylphenidate, modafinil, and atomoxetine (45,67,127,128). The SSRT is under probable noradrenergic control and has been reported to be behaviorally unaffected by manipulations of the serotonin and dopamine systems in animals and in man (12,105). Notably, ADHD studies in the current review showed consistent beneficial effects of methylphenidate, atomoxetine, and modafinil on SSRT. In healthy volunteers, one study reported beneficial effects of modafinil on SSRT, whereas another did not, while the two available atomoxetine studies reported significant benefits. There were no healthy volunteer methylphenidate studies using the SST.

Planning activities in advance is often difficult for people with ADHD. Indeed, patients with ADHD showed medium deficits in executive planning, as indexed by SOC and its variants, in our meta-analysis of the literature ($d = .491$). These findings accord well with a previous meta-analysis comparing ADHD with control subjects on executive planning tasks (effect sizes of .51 and .69 depending on the precise task [110]). Executive planning is impaired by frontal lesions, and functional imaging has likewise demonstrated this domain to be dependent on distributed frontostriatal circuitry, notably the lateral prefrontal cortices (27,129). In healthy volunteers, modafinil improved planning performance by reducing the number of attempts required to obtain correct solutions at hard levels of difficulty in two studies; three other studies, however, found no significant benefits. In children with ADHD, no significant benefits of methylphenidate on planning were found, while a single adult patient study did report significant improvements. Modafinil improved executive planning in adults with ADHD (one available study), whereas atomoxetine did not (ditto). Guanfacine improved executive planning in healthy control subjects in one study.

Set shifting as indexed by IDED task errors was significantly impaired in ADHD versus control subjects in the meta-analysis but with a small effect size (effect size .160), suggesting that this function is relatively spared compared with response inhibition, spatial working memory, and executive planning. An effect size of .46 was reported for ADHD versus control subjects on the related Wisconsin Card Sort Test, in terms of perseverative errors (110). Meta-analysis indicated no significant effects of modafinil on IDED performance in healthy control subjects. In healthy human volunteers, methylphenidate significantly improves extradimensional shifting—a result that could be attributed to effects on either dopamine or noradrenaline or both. However, in a recent positron emission tomography study, it was shown that methylphenidate could impair probabilistic reversal learning in those subjects with the highest displacement of striatal raclopride, suggesting that excessive striatal DA may impair reversal learning (100). Significantly, in terms of ADHD, such effects occurred in those subjects who scored least on the Barratt Impulsivity Scale. The most impulsive individuals generally exhibited improvements with methylphenidate on reversal learning; hence, we would predict such "attentional sticking" effects of methylphenidate to be a function of dose and severity of ADHD symptoms.

It is probable that there exists an optimal level of neurotransmitter for a given function in an individual. Baseline dependency is thus critical, and this is suggested by the literature (97). For example, in a placebo-controlled healthy volunteer study, the dopamine D2 receptor agonist bromocriptine (2.5 mg) impaired cognitive performance (Wisconsin Card Sort and Fan Effect tasks) in subjects with high baseline memory span, while improving performance in low-span baseline memory span subjects (130). In a double-blind placebo-controlled healthy volunteer study, it was found that the effects of modafinil (400 mg) and methylphenidate (40 mg) on perceptual processing speed were dependent on baseline function: enhancement was principally seen in subjects with low baseline (placebo) performance (131). There is also evidence from a study in healthy volunteers that the effects of different doses of amphetamine (2.5–12.5 mg) on frontal brain activation during a working memory functional imaging task operated according to an inverted U function (132). The cognitive effects of medications such as methylphenidate, modafinil, and atomoxetine are likely to be contingent on baseline performance (and implicitly, baseline levels of neurotransmitter activity). This may account for the more consistent drug effects found in patients with ADHD, who have relatively low baseline performance and putatively impaired dopamine/noradrenaline transmission.

Dopamine and noradrenaline are likely to have somewhat distinct roles in cognition because of the nature of their innervation of forebrain structures. For example, the ascending noradrenergic projections have only a relatively sparse innervation of the basal ganglia compared with those for dopamine, including the striatal regions intimately associated with the initiation of behavior and incentive motivational processes. By contrast, these transmitters have complementary roles in cognition controlled by such structures as the prefrontal cortex where their inputs do overlap (50). These complementary roles are illustrated by their relative effects on signal-to-noise processing in working memory paradigms (50), by their apparently contrasting effects on set-formation (dopamine) and extradimensional set shifting (dopamine and noradrenaline) (63), and on inhibitory response control in tasks such as stop-signal inhibition and go no/go paradigms where noradrenergic agents such as atomoxetine appear to have greater efficacy (e.g., [67]).

Limitations

This article is selective in that it focuses on a subset of CANTAB tests and so findings may not generalize to other paradigms. We focused on this battery given its relatively widespread use in ADHD research and its application in translational and back-translational

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work described. Though caution is required when attempting to generalize between different batteries, the effect sizes from CANTAB meta-analysis are broadly comparable in magnitude with those reported in meta-analyses that have included various other cognitive tests (9,10,18,110). Many of the identified data articles herein have been written by people within our group, who have also played key roles in the development, validation, and deployment of commercial CANTAB tests. This represents a potential conflict of interest that we fully disclose. It will be important for findings to be independently replicated by other groups in time, and we welcome such endeavors. Other potential limitations, e.g., relating to test-retest properties (133), are outlined in Supplement 1.

Conclusions

Patients with ADHD demonstrate medium to large decrements in performance on standardized CANTAB cognitive assessments of response inhibition, working memory, executive planning, and a small decrement in attentional set shifting. Such tests show sensitivity to the amelioration of cognitive dysfunction by pharmacotherapy, more consistently in patients than in control subjects, although more data are needed to allow formal meta-analysis of most drug effects. Nonetheless, relatively small-scale proof-of-concept trials, viewed alongside translational studies, have shed considerable light on the mechanisms by which pharmacotherapies exert their beneficial effects on dissociable aspects of cognition and by extension, clinical ADHD symptomatology, via modulation of noradrenergic and dopaminergic pathways. Cognitive tests such as those considered here will be useful in the future evaluation of preexisting and novel agents in healthy volunteers, ADHD, and other clinical disorders associated with overlapping cognitive problems (e.g., schizophrenia [134]). The utility of the tests is also underlined by a review of the translational and back-translational potential of the battery for studies in rodents and nonhuman primates.

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SRC, TWR, and BJS consult for Cambridge Cognition. JHB and ADB are employees of Cambridge Cognition. SRC additionally consults for P1Vital and Shire. TWR additionally consults for Pfizer, Eli Lilly, Lundbeck, Roche, and Allon Therapeutics and has received research grants from GlaxoSmithKline, Lilly, and Pfizer. BJS additionally consults for Novartis, Shire, GlaxoSmithKline, Lilly, and Boehringer-Ingelheim. UM has received research and educational grant support from Janssen-Cilag and honoraria or travel expenses from Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pharmacia-Upjohn, and UCB Pharma. SW-R reports no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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