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Methylphenidate ('Ritalin') can Ameliorate Abnormal Risk-Taking Behavior in the Frontal Variant of Frontotemporal Dementia

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The frontal variant of frontotemporal dementia is a significant neurological condition worldwide. There exist few treatments available for the cognitive and behavioural sequelae of fvFTD. Previous research has shown that these patients display risky decision-making, and numerous studies have now demonstrated pathology affecting the orbitofrontal cortex. The present study uses a within-subjects, double-blind, placebo-controlled procedure to investigate the effects of a single dose of methylphenidate (40 mg) upon a range of different cognitive processes including those assessing prefrontal cortex integrity. Methylphenidate was effective in 'normalizing' the decision-making behavior of patients, such that they became less risk taking on medication, although there were no significant effects on other aspects of cognitive function, including working memory, attentional set shifting, and reversal learning. Moreover, there was an absence of the normal subjective and autonomic responses to methylphenidate seen in elderly subjects. The results are discussed in terms of the 'somatic marker' hypothesis of impaired decision-making following orbitofrontal dysfunction.
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INTRODUCTION

The frontal variant of frontotemporal dementia (fvFTD) is a clinically significant neurological problem that constitutes one of the most prevalent forms of early-onset dementia (Ratnavalli *et al*, 2002). There currently exist few treatments available for the amelioration of the cognitive and behavioral deficits in fvFTD, in stark contrast to the management options for dementia of the Alzheimer type (Rahman *et al*, 2000). An initial study by Coull *et al* (1996) showed that the α_2 noradrenergic antagonist idazoxan produced cognitive improvements in patients with fvFTD on tests of planning, sustained attention, verbal fluency, and episodic memory. Idazoxan was thought to increase coerulo-cortical noradrenaline (NA) activity via presynaptic effects. There has also been some interest in using selective serotonin reuptake inhibitors (SSRIs) in the treatment of frontotemporal dementia, but we have previously found little objective benefit of a chronic dosage regimen of paroxetine (Deakin *et al*, 2004a).

Previous work has demonstrated that the psychostimulant methylphenidate (Ritalin) improves higher level cognitive function in healthy volunteers, on tests of working memory and planning (Elliott *et al*, 1997; Mehta *et al*, 2000). Methylphenidate increases synaptic and extracellular concentrations of dopamine (DA) and NA (Scheel-Krüger, 1971) via blockade of the reuptake transporters in the striatum (Volkow *et al*, 1998). There has been historical interest in methylphenidate, as it has been used for many years in the treatment of attention-deficit hyperactivity disorder (ADHD) and disorders of sleep and arousal such as narcolepsy (Aron *et al*, 2003; Conners and Eisenberg, 1963). The cognition-enhancing effects of methylphenidate have been investigated in patients with brain injury, with some studies demonstrating improvements (Gualtieri and Evans, 1998; Plenger *et al*, 1996; Whyte *et al*, 1997), but others failing to find beneficial effects (Speech *et al*, 1993; Williams *et al*, 1998). Methylphenidate has been studied as an adjuvant medication for the treatment of depression and apathy in various disorders (Marin *et al*, 1995; Chatterjee and Fahn, 2002). Analyses of the neurochemical correlates of FTD based on autopsy tissue have generally implicated deficits in DA and NA neurotransmission (Bettendorff *et al*,

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1997; Francis *et al*, 1993; Gilbert *et al*, 1988; Nagaoka *et al*, 1995; Sjogren *et al*, 1998; Sparks and Markesbery, 1991). For example, Sjogren *et al* (1998) reported a significant reduction in the CSF concentration of homovanillic acid, a major metabolite of DA, in a large sample of frontotemporal dementia cases. This indication of DA pathology in fvFTD highlights the therapeutic potential of methylphenidate in this condition.

We originally proposed that the orbitofrontal cortex was a major locus of aberrant function in fvFTD (Rahman *et al*, 1999; Mendez and Cummings, 2003). Neurocognitive assessment indicated risk-taking behavior in the domain of decision-making and deficits in reversal learning, which resemble the cognitive sequelae of orbitofrontal cortex lesions (Damasio, 1996; Rolls *et al*, 1994). These reward-based deficits are considered to be one of the main problems that fvFTD patients face (La Coco and Nacci, 2004), in contrast to the episodic memory dysfunction found in the dementia of Alzheimer type (eg Lee *et al*, 2003). Neuroanatomical evidence for orbitofrontal dysfunction has been borne out in subsequent post mortem and *in vivo* neuroimaging studies (Ibach *et al*, 2004; Liu *et al*, 2004; Diehl *et al*, 2004; Kobayashi *et al*, 1999). For example, a European multicentre PET study showed that the ventromedial frontopolar cortex was critically affected in every one of 29 fvFTD cases (Salmon *et al*, 2003).

The ascending mesocorticolimbic DA projection into the prefrontal cortex has a critical role in signaling reward-related information (Hollerman and Schultz, 1998), and a fronto-striatal circuit comprising the ventral striatum and orbitofrontal cortex has been implicated in a range of emotional processes and affective disorders (Alexander *et al*, 1986; Mega and Cummings, 1994). We hypothesized that methylphenidate would ameliorate reward-based deficits in fvFTD by stimulating dopaminergic transmission in orbitofrontal fronto-striatal circuitry. We have previously reported no significant effects on decision-making cognition in healthy elderly volunteers receiving a single 40 mg dose of methylphenidate (Turner *et al*, 2003). However, healthy elderly volunteers tend to be more conservative and show reduced risk-taking behavior compared to young adults (Deakin *et al*, 2004b), whereas fvFTD patients show increased risk-taking behavior compared to age-matched controls (Rahman *et al*, 1999). The present study sought to explore the cognition-enhancing properties of methylphenidate in fvFTD on a neuropsychological assessment focusing on measures of prefrontal cortical function, including reward-based learning and working memory, and temporal lobe memory function (visual recognition memory).

METHODS

Participants

Eight patients were recruited with a clinical diagnosis of fvFTD according to the Lund and Manchester Groups (1994) criteria. The eight patients are labelled A-H in Figure 1. A full medical history was taken prior to testing by specialist registrar in neurology (PJN). Patient B was female; the rest were male. Patients were all Caucasian, with a mean age of 62.0 years (SD 10.1). Four patients were current smokers (A, B, F, H). The Mini Mental State Examination (MMSE; Folstein *et al*, 1975) was administered with an exclusion threshold of 20, which would preclude computerized assessment (mean score 27.0, SD 1.7). Premorbid verbal intelligence was assessed with the National Adult Reading Test (mean 110.7, SD 6.2). Subjects were asked to abstain from alcohol intake on the evenings before test sessions or excessive caffeine intake on the mornings of test sessions. Possible risks and benefits were explained to all patients and caregivers before seeking informed consent for the study. The study was approved by the Cambridge Local Research Ethics Committee and the Department of Health Medicines Controls Agency. Patients were excluded if the severity of dementia precluded computerized neuropsychological assessment (MMSE <20), or if they suffered from concomitant illness likely to confound the interpretation of findings. Five patients were currently receiving medication: atenolol 25 mg/day (patient H), vitamin E tablets (patient F), a nonsteroidal anti-inflammatory drug (patient A), chlorpromazine 150 mg/day, fluoxetine 20 mg/day and diazepam 15 mg/day (patient B), and hormone replacement therapy and diclofenac (patient C). A total of 11people were originally screened for the study, of which three were excluded from participating in the study, due to concomitant illnesses, which contraindicated the use of methylphenidate (glaucoma, unstable hypertension, and stable/unstable angina).

Procedure

This study followed a double-blind, placebo-controlled cross-over design. In this design, the performance of each subject is measured twice, once following administration of an active drug and once following administration of a placebo. The two test sessions for each subject were separated by 1–2 weeks and treatment order was fully counter-balanced across subjects. The groups that had taken drug first (A, D, F, H) or placebo first (B, C, E, G) were matched for age, MMSE, and NART IQ estimate (age: $F(1,6)=0.215$, $P=0.659$; MMSE: $F(1,6)=0.667$, $P=0.445$; NART: $F(1,6)=2.48$, $P=0.166$). All test sessions were in the afternoon, with ingestion of the drug or placebo at approximately 1430 hours. A 40 mg dose of methylphenidate was used, with cognitive testing commencing at 90 min after administration (for about 2 h). Peak plasma concentrations of methylphenidate are reached approximately 2 h after ingestion (half-life in plasma 1–2 h, mean systemic clearance is 10 l/h/kg) (Gilman *et al*, 1980; see also Turner *et al* (2003) and Muller *et al* (2005) for older healthy adults). Adverse effects during the session were monitored and recorded, with particular care to identify any nervousness, headache, and gastrointestinal disturbances. Blood pressure was measured using a traditional sphygmomanometer immediately prior to ingestion of the tablet, and just prior to cognitive testing (at +90 min). Visual analog scales (Bond and Lader, 1974) were administered prior to tablet ingestion and just prior to cognitive testing, for the scales alert–drowsy, calm–excited, strong–feeble, muzzy–clear headed, well coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–

amicable,
interested–bored and withdrawn-gregarious. A restricted threshold of $P = 0.01$ was set to represent a significant difference between scores in order to reduce the chance of a type I error.

Cognitive Assessment

In both test sessions, the patients were given the same assessment in a fixed order, consisting of a computerized assessment including established tasks from the CANTAB battery (www.camcog.com): pattern recognition memory, spatial recognition memory, spatial span, spatial working memory, and ID/ED attentional set-shifting (see Rahman *et al*, 1999 for descriptions). The one-touch version of the CANTAB Tower of London test of spatial planning was also administered (Owen *et al*, 1995). Finally, the Cambridge Gamble Task (Rogers *et al*, 1999) was used to assess decision-making cognition. In this task, subjects are presented with an array of 10 red or blue boxes on each trial. The ratio of red : blue boxes varies across trials in a pseudo-random sequence (6 : 4, 7 : 3, 8 : 2, 9 : 1). The subject is informed that the computer has hidden a token, at random, under one of the boxes, and they must decide whether the token is hidden under a red or a blue box. After making this probabilistic judgment (they should always select the color in the majority), subjects must place a bet on their confidence in the decision. Bets are generated by the computer in either an ascending or descending sequence, with the available bets in percentages of the current points total (5, 25, 50, 75, and 95%). After the bet is placed, the location of the token is revealed and the points bet are either added or deducted from the running total. Subjects perform four blocks of 10 trials in each condition (ascending or descending bets), where at the start of each block the subject returns to 100 points.

Statistical Analysis

Statistical analyses were run in SPSS version 9.0 with two-tailed statistics thresholded at $P < 0.05$. In the crossover design, it is the difference between the two test sessions that denotes the effect of the treatment. Given the small group sizes, data were analyzed using nonparametric statistics. Drug effects were tested by comparing the methylphenidate and placebo scores within-subjects using a Wilcoxon signed-ranks test (as described in Howell, 1997). This test is a distribution-free analog for related samples.

RESULTS

Cognitive Assessment

Neuropsychological performance is shown in Table 1. There were no effects of methylphenidate on pattern recognition memory, spatial recognition memory, spatial working memory, ID/ED attentional set-shifting, and one-touch Tower of London tasks. A marginally significant (detrimental) effect on spatial span on the span score ($P = 0.096$) was not apparent on usage errors on this task ($P = 0.612$).

Table 1 Neuropsychological Performance of fvFTD Patients after Methylphenidate (MPH) and Placebo (Mean (SD))

	MPH	Placebo	Wilcoxon z-value
Pattern recognition memory			
Percentage correct	17.9 (2.2)	19.4 (3.3)	$Z = -1.28$, $P = 0.201$
Latency (ms)	3270 (674)	3490 (1480)	$Z = -0.560$, $P = 0.575$
Spatial recognition memory			
Percentage correct	14.0 (3.0)	13.6 (3.5)	$Z = -0.736$, $P = 0.461$
Latency (ms)	3230 (908)	3570 (346)	$Z = -0.280$, $P = 0.779$
Spatial span			
Span	4.25 (0.71)	4.88 (0.64)	$Z = -1.67$, $P = 0.096$
Errors	2.52 (0.70)	2.72 (1.25)	$Z = -0.507$, $P = 0.612$
Spatial working memory			
Total between-search errors	52.6 (21.6)	48.2 (26.9)	$Z = -0.840$, $P = 0.401$
Strategy score	37.9 (3.6)	36.5 (3.3)	$Z = -0.916$, $P = 0.360$
ID/ED attentional set shifting			
ID stage errors	1.63 (3.81)	1.50 (2.27)	
ED stage errors	10.8 (12.0)	9.88 (10.0)	[a]$Z = -0.314$, $P = 0.753$
Reversal errors	14.8 (16.8)	14.2 (14.9)	
Nonreversal errors	7.17 (5.27)	10.3 (7.92)	[b]$Z = -0.105$, $P = 0.917$
One-touch tower of London			
Mean attempts (2 moves)	1.36 (0.748)	1.29 (0.756)	
Mean attempts (3 moves)	1.29 (0.393)	1.21 (0.567)	
Mean attempts (4 moves)	1.54 (0.366)	1.85 (0.627)	
Mean attempts (5 moves)	2.21 (0.940)	2.14 (0.643)	[c]$Z = -0.406$, $P = 0.684$
Mean latency (2 moves) (s)	13.7 (8.7)	15.9 (20.0)	
Mean latency (3 moves) (s)	20.9 (17.2)	30.6 (38.4)	
Mean latency (4 moves) (s)	43.5 (27.0)	42.7 (26.5)	
Mean latency (5 moves) (s)	59.4 (34.4)	70.1 (47.0)	[d]$Z = -0.338$, $P = 0.735$

ID = intradimensional shift, ED = extradimensional shift.
[a]The difference between ED errors and ID errors was tested.
[b]The difference between reversal and nonreversal errors was tested.
[c]The average mean attempts across all levels of difficulty was tested.
[d]The average latency across all levels of difficulty was tested.

Data for the Cambridge Gamble Task are shown in Figures 1 and 2. There were no effects of methylphenidate on the average deliberation time ($Z = -0.280$, $P = 0.779$) or choice of the likely outcome ($Z = -0.170$, $P = 0.865$) (see Figure 2). The difference in betting behavior (Figure 1) in the drug and placebo conditions was statistically significant ($Z = -2.38$, $P = 0.017$), with patients demonstrating reduced betting on methylphenidate. This was a consistent effect across all eight patients. To further evaluate the changes in betting behavior on methylphenidate, a two (drug: methylphenidate, placebo) $\times$ 2 (condition: ascend, descend) $\times$ 4 (ratio: 9 : 1, 8 : 2, 7 : 3, 6 : 4) $\times$ 2 (order of drug administration) mixed-model ANOVA was performed. There was a significant main effect of drug ($F_{1,6} = 7.73$, $P = 0.032$),

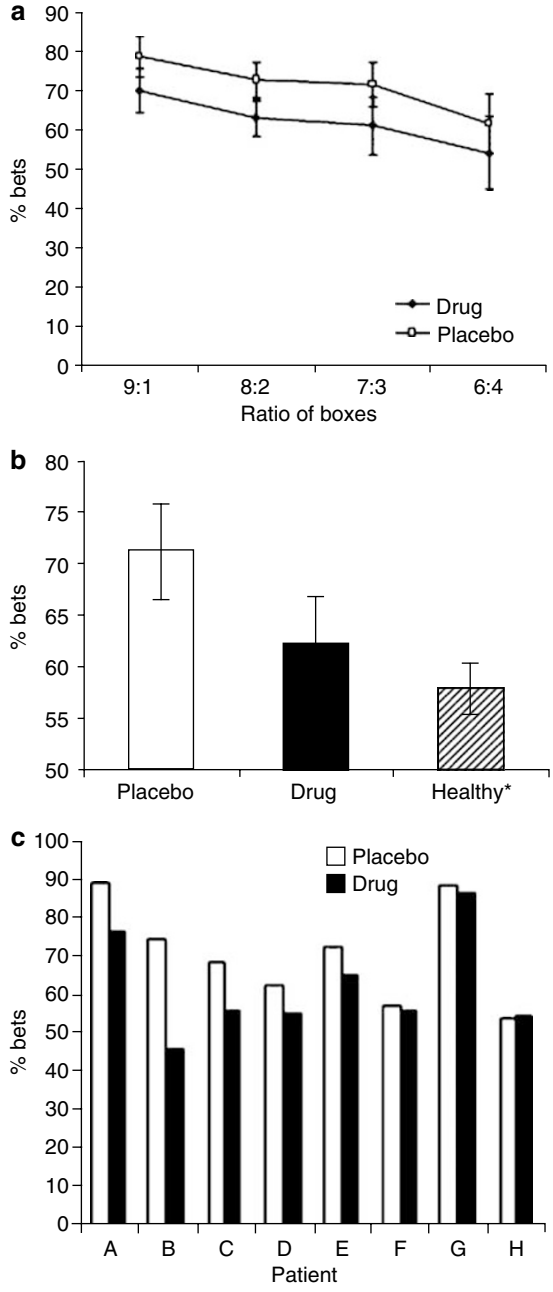

Figure 1 (a) Methylphenidate significantly reduced betting behavior on the Cambridge Gamble Task. Error bars indicate the standard errors of the mean. (b) The reduction in betting behavior in fvFTD patients on methylphenidate normalizes task performance, that is, performance approaches of healthy older adults. *Healthy data from the placebo condition of Turner *et al* (2003), in 20 male volunteers aged 55–69 years (mean age 61 years). (c) Individual data in the fvFTD group show that the reduction in betting is apparent in every subject.

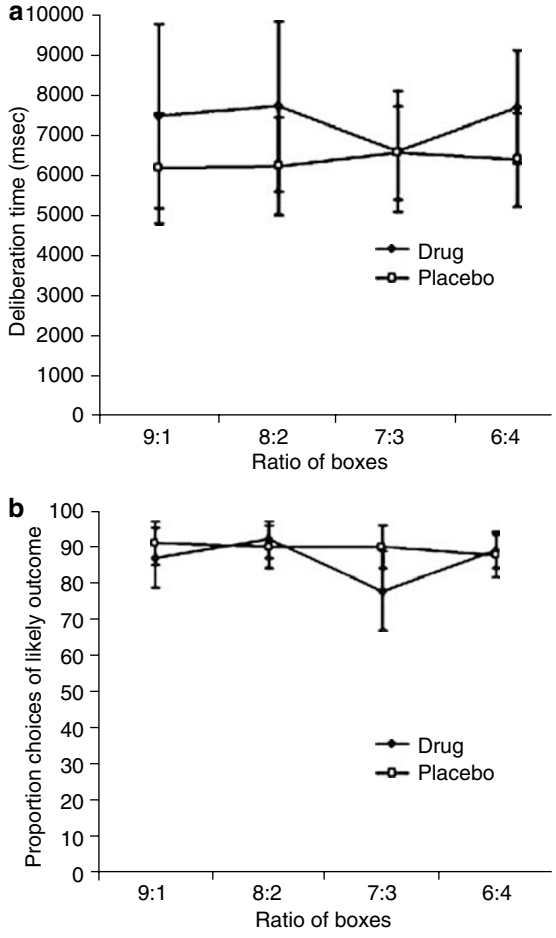

Figure 2 Methylphenidate treatment did not significantly affect deliberation times (a) or choice of most likely outcome (b) on the Cambridge Gamble Task.

supporting the effect in the nonparametric test. The main effects of order ($F_{1,6} = 0.570$, $P = 0.479$) and drug × order interaction term ($F_{1,6} = 1.37$, $P = 0.287$) were both nonsignificant. The main effect of condition ($F_{1,6} = 1.60$, $P = 0.253$) was not significant, although, on average, subjects did place higher bets in the descend condition than in the ascend condition (methylphenidate: ascend mean = 58.8 (SD 22.0), descend mean = 65.5 (SD 19.8); placebo: ascend mean = 66.5 (SD 22.8), descend mean = 75.9 (SD 13.0)), consistent with previous studies using the Cambridge Gamble Task (eg Clark *et al*, 2003; Mavaddat *et al*, 2000). Similarly, the main effect of ratio was not significant (Greenhouse–Geisser correction $F_{1.42,8.52} = 2.17$, $P = 0.177$), although, on average, subjects placed higher bets at the 9 : 1 ratio compared to the 6 : 4 ratio (see Figure 1). All interaction terms in the ANOVA model were nonsignificant ($P > 0.10$).

Cardiovascular and Subjective Measures

Cardiovascular measures at baseline and prior to cognitive testing are shown in Table 2. Baseline measurements of pulse ($Z = -0.632$, $P = 0.528$) and systolic blood pressure ($Z = -1.20$, $P = 0.231$) did not differ significantly between drug and placebo sessions, although the baseline measurements of diastolic blood pressure approached significance ($Z = -1.87$, $P = 0.061$). There was no overall difference in pulse (ie change from baseline) for the drug condition compared to the placebo condition ($Z = -0.943$, $P = 0.345$). While there was a general increase in blood pressure after methylphenidate, the differences in systolic and diastolic

Table 2 Cardiovascular Measures of Pulse, Systolic Blood Pressure (bp), and Diastolic Blood Pressure (bp) on Drug and Placebo Sessions (Mean (SD))

	Methylphenidate		Placebo	
	Baseline	**Pretesting**	**Baseline**	**Pretesting**
Pulse	77.2 (11.9)	84.5 (14.9)	72.9 (15.3)	73.1 (10.7)
Systolic bp	132 (12.1)	140 (14.6)	140 (18.2)	138 (19.3)
Diastolic bp	76.8 (9.79)	86.1 (9.88)	85.4 (6.84)	84.3 (11.4)

blood pressure for the drug condition compared to the placebo condition approached significance (systolic blood pressure: $Z=-1.78$, $P=0.075$; diastolic blood pressure: $Z=-1.78$, $P=0.075$). However, these comparisons were nonsignificant when the subject receiving atenolol was excluded from the analysis (systolic blood pressure $Z=-1.48$, $P=0.138$; diastolic blood pressure $Z=-1.58$, $P=0.115$). For the visual analog scales, the change from baseline score was calculated for each drug session. There was no effect of drug on any of these changes compared to placebo.

DISCUSSION

This study reported the effects of methylphenidate upon subjective mood, cardiovascular activity, and a range of cognitive functions in patients with fvFTD. The key finding was an attenuation of risk-taking following methylphenidate, on a laboratory measure of decision-making (the Cambridge Gamble Task). This was a relatively selective effect: there were no significant effects of drug treatment on tasks of memory function associated with temporal lobe integrity (recognition memory) or executive tasks associated with dorsolateral prefrontal function (planning, extra-dimensional shifting and working memory). In a previous study of methylphenidate effects in healthy older adults (aged 55–69 years, mean age = 61 years), we did not detect any significant effects of this medication on risk-taking on the Cambridge Gamble Task (Turner *et al*, 2003). We infer that the significant effect of methylphenidate on risk-taking in patients with fvFTD is associated with the behavioral disturbance induced by the dementia. This effect also shows some neurochemical specificity: we have shown previously that chronic treatment with the selective SSRI paroxetine did not affect performance on the Cambridge Gamble Task in an independent group of fvFTD patients (Deakin *et al*, 2004a). The amelioration of risk-taking behavior in fvFTD by methylphenidate carries important implications for rehabilitative approaches, given that neurobehavioral deficits including risky behavior and disinhibition represent a significant barrier for social interaction and everyday functioning within society.

Under baseline conditions, we have shown previously that patients with fvFTD displayed increased betting behavior on the Cambridge Gamble Task compared to matched healthy controls (Rahman *et al*, 1999). This increased betting was apparent across all ratios of boxes, in both the ascending and descending conditions of the task (Rahman *et al*, 1999). The action of methylphenidate in the present study was to normalize risk-taking behavior, bringing the fvFTD patients toward the typical performance of healthy older adults (see Figure 1b, with healthy performance taken from Turner *et al* (2003)). The order of drug administration was fully counter balanced and order did not have a significant effect in the analysis of betting performance. The discrepancy between the ascending and descending conditions on the Cambridge Gamble Task can provide an index of impulsivity or delay aversion. Impulsive or impatient subjects are expected to place high bets in the descend condition but low bets in the ascend condition, whereas a genuine risk-preferent subject would wait in order to place high bets in the ascend condition (see Cools *et al*, 2003). In the present study, the effect of methylphenidate to reduce betting did not interact with the ratio of boxes, and did not interact with the ascend *vs* descend betting condition. As such, it seems unlikely that the normalizing effect of methylphenidate results from an 'antiimpulsive' action similar to that seen in ADHD (Aron *et al*, 2003; Tannock *et al*, 1989).

The beneficial effects of methylphenidate on decision-making in fvFTD may be mediated at the level of the orbitofrontal cortex, the striatum, or the connectivity between these two regions. Neuropathology in the orbitofrontal cortex is a consistent feature of fvFTD (eg Salmon *et al*, 2003) and is thought to underlie the risk-taking behavior seen under baseline conditions (Rahman *et al*, 1999). However, the DA transporters that are targeted by methylphenidate are located predominantly within the striatum. The DA projection from the midbrain to the ventral striatum is known to signal reward-related information (Schultz, 2002): specifically, the temporal discrepancy between the occurrence and the prediction of reward (the reward prediction error) (Hollerman and Schultz, 1998). It is possible that neuropathology affecting the DA system in fvFTD (eg Sjogren *et al*, 1998) may increase reward-driven behavior under baseline conditions. Stimulation of DA neurotransmission by methylphenidate may conceivably normalize these changes. In addition, DA stimulation by methylphenidate appears to modulate orbitofrontal cortex activity: methylphenidate administration significantly increased glucose metabolism in the orbitofrontal cortex of cocaine addicts (Volkow *et al*, 2005), who also display increased risk taking (Bartzokis *et al*, 2000). These increases in orbitofrontal metabolism were correlated with methylphenidate-induced changes in thalamic DA binding, suggesting a modulatory role of the mesothalamic DA projection (Volkow *et al*, 2005).

An alternative explanation is that the effect on decision-making cognition may reflect the action of methylphenidate to produce or modulate central 'somatic markers' (Damasio, 1996) via stimulation of the ascending catecholamine systems. Through connectivity with the amygdala and somatosensory cortex, the orbitofrontal cortex may contribute to decision-making by retrieving somatic information associated with the outcomes of similar decisions in the past (Bechara, 2003; Bechara *et al*, 2003; Damasio, 1996). These somatic states facilitate an exhaustive cost–benefit analysis of decision-making. The amygdala may predominantly mediate the elicitation of emotional responses by conditioned or unconditioned stimuli ('primary inducers'),

whereas the orbitofrontal cortex elicits emotional arousal by thoughts, memories, and hypothetical decisions ('secondary inducers') (Bechara *et al*, 2003). Via dopaminergic innervation of the orbitofrontal cortex (Oades and Halliday, 1987) and amygdala (Fallon *et al*, 1978), methylphenidate may modulate or mimic these somatic representations in a decision-making context.

Dysfunction in somatic- and emotion-related circuitry may also impair the monitoring of internal state. In the present study, we were unable to demonstrate any significant effects of methylphenidate on subjective mood. This is perhaps remarkable in itself: in previous research, methylphenidate robustly increased subjective ratings of alertness and energy in healthy volunteers (Elliott *et al*, 1997; Heishman and Henningfield, 1991), including elderly volunteers (Turner *et al*, 2003). The lack of subjective effects in fvFTD implies that these patients are unable to sense differences in their internal state following drug administration. The cardiovascular effects of methylphenidate were unclear in the present study. There was a subtle effect of methylphenidate to increase systolic and diastolic blood pressure. However, this effect only reached trend levels of significance. In addition, baseline diastolic blood pressure was somewhat lower on the methylphenidate session, and therefore, we cannot rule out a regression to the mean effect. Future research is needed in a larger group of patients to confirm whether there is a genuine dissociation between the subjective and cardiovascular effects of methylphenidate in fvFTD patients.

Economic models distinguish decision-making under risk (when outcome probabilities are explicit) from decision-making under ambiguity (when outcome probabilities are undefined) (Ellsberg, 1961; Smith *et al*, 2002). Bechara *et al*, (2001) and Bechara (2003) have recently investigated the effects of a DA manipulation on the Iowa Gambling Task. On this task, subjects make a series of choices from four decks of cards that vary in the magnitude and frequency of winning and losing. Subjects are provided with no information about the differing contingencies of the four decks; consequently, the early stages of the task emphasize decision-making under ambiguity. Bechara *et al* (2001, 2003) reported bidirectional modulation of choice behavior by the dopaminergic agents dextroamphetamine and haloperidol, but these effects were restricted to the early part of the task when outcome probabilities were not well defined. In contrast, the modulatory effects of methylphenidate on the Cambridge Gamble Task suggest that DA predominantly manipulates decision-making under risk, as this task explicitly presents trial-by-trial probabilities. However, it is possible that the cognitive impairment present in these fvFTD patients may have affected their explicit knowledge of risk on the Cambridge Gamble Task, and as such, these decisions may have also been made under ambiguity.

In the present study, there was no effect of methylphenidate on reversal learning on the ID/ED task. Reversal learning is also robustly linked to orbitofrontal integrity (Clark *et al*, 2004) and was impaired in fvFTD patients in our previous investigation (Rahman *et al*, 1999). This suggests some parcellation at a neurochemical level within the orbitofrontal cortex. These data are consistent with accumulating evidence using a marmoset analog of the ID/ED task, showing that reversal learning is sensitive to prefrontal 5-HT depletion but not prefrontal DA depletion (Clarke *et al*, 2004; Crofts *et al*, 2001). The lack of effect of methylphenidate on traditional measures of executive function, including working memory and planning, suggests a practical limitation on the use of this agent to treat cognitive dysfunction in fvFTD. It is notable that the level of performance of the patients in the present study was somewhat more impaired than that of the mild patients reported previously (Rahman *et al*, 1999). Mild cases may stand to benefit more from cognition-enhancing medication. A previous study by Coull *et al* (1996) showed that idazoxan, an α_2 NA antagonist that acts presynaptically to elevate NA activity, produced several instances of cognitive improvement in fvFTD, but impaired spatial working memory. Recent neuropathological findings support the notion that NA neurotransmission is abnormal in fvFTD, with levels reduced by at least 30% in the nucleus basalis, thalamus, locus coeruleus, and amygdala (Nagaoka *et al*, 1995). It is possible that some cognitive effects associated with DA or NA challenges may be cancelled out by the combined actions of methylphenidate on catecholamine neurotransmission. Future research may utilize more selective DA agents such as the D2 agonist bromocriptine. Some further limitations of the present study are the small number of participants, the use of an acute (ie single dose) study design, and the presence of additional medications in five of the eight patients, which may interact with the effects of methylphenidate. These encouraging findings must be treated as preliminary and require extension and replication in a larger sample size with a chronic treatment design.

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