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ORIGINAL INVESTIGATION

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Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial

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Abstract *Rationale:* Patients with frontal variant frontotemporal dementia (fvFTD) present with disinhibition, impulsiveness, apathy, altered appetite and stereotypic behaviors. A non-randomized clinical trial found improvement in these symptoms after treatment with a selective serotonin reuptake inhibitor (SSRI). *Objectives:* We aimed to subject a SSRI, paroxetine, to a more rigorous test of its efficacy using a double-blind, placebo-controlled experimental design. *Methods:* Ten subjects meeting the consensus criteria for FTD were entered into a double-blind, placebo-controlled crossover trial. Doses of paroxetine were progressively increased to 40 mg daily. The same regimen was used for placebo capsules. Subjects were assessed with a battery of cognitive tests in the sixth week of paroxetine and placebo treatment. At each assessment, caregivers were interviewed using the Neuropsychiatric Inventory and asked to complete the Cambridge Behavioral Inventory. *Results:* There were no significant differences on the Neuropsychiatric Inventory or the Cambridge Behavioral Inventory. Paroxetine caused a decrease in accuracy on the paired associates learning task, reversal learning and a delayed pattern recognition task. There were no changes on the decision-making task, in spatial span, spatial recognition, spatial working memory, digit span and verbal fluency. *Conclusions:* This study finds no evidence for the efficacy of paroxetine in the treatment of fvFTD. The results suggest that a chronic course of paroxetine may selectively impair paired associates learning, reversal learning and delayed pattern recognition. This pattern of deficits closely resembles that seen after tryptophan depletion. Results are discussed with respect to current theories on serotonergic modulation of orbitofrontal/ventromedial prefrontal cortex.

Keywords Decision-making · Frontotemporal dementia · Paroxetine · Serotonin

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Introduction

Frontotemporal dementia (FTD) is the term now preferred to describe non-Alzheimer-type dementia affecting the frontal and/or anterior temporal lobes (Hodges and Miller 2001). FTD typically occurs at a younger age than most dementias, when patients still have parental and financial responsibilities for children. The prevalence in the under-65 s is almost equal to Alzheimer's disease (Ratnavalli et al. 2002). FTD represents a continuum: at one end is the temporal form, known more commonly as semantic dementia, and, at the other end, the frontal variant of FTD (fvFTD) (Orrell and Sahakian 1991). fvFTD is characterized by profound changes in personality and social behavior with stereotypic ritualistic behavior (Bozeat et al. 2000; Neary et al. 2000). Patients may ignore visitors, or address them rudely, and may fail to offer food and drink to others, they may also make personal comments within earshot of strangers (Plaisted and Sahakian 1997). Changes in mood and apathy are common and many patients develop an increased desire for sweet food coupled with reduced satiety. This can result in considerable weight gain and caregivers are often led to ration food. The loss of concern and empathy for family and friends places a great emotional burden on caregivers.

Impaired serotonin (5-HT) function has been implicated in the pathogenesis of depression, anxiety, obsessional–compulsive and eating disorders (Mann 1999). Drugs such as the selective serotonin reuptake inhibitors (SSRIs), which decrease 5-HT re-uptake, are particularly effective in the treatment of these symptoms (Blier and de Montigny 1999). There is also increasing evidence that reduced 5-HT function is involved in impulsive behavior

in antisocial individuals (Dolan et al. 2001). One study in post-mortem brains reported reductions in post-synaptic 5-HT receptor binding in the frontal lobes of patients who died in the early stages of FTD (Sparks and Markesbery 1991). This raises the possibility that impaired 5-HT function contributes to the pathogenesis of some symptoms in fvFTD and that SSRIs might ameliorate such symptoms.

A further rationale for investigating the effect of a SSRI in fvFTD comes from recent evidence that changes in 5-HT function may specifically alter performance on neuropsychological tasks mediated by orbitofrontal and not dorsolateral circuitry (Robbins 2000; Rogers and Robbins 2001), the same circuitry that has been specifically implicated in fvFTD. Normal volunteers who have undergone acute tryptophan depletion, which acutely reduces central 5-HT, demonstrate the same deficits on reversal learning as seen in fvFTD (Rahman et al. 1999; Rogers et al. 1999a). This same deficit is also seen in patients with damage to the orbitofrontal cortex (OFC) but not the dorsolateral cortex (DLPFC) (Rogers et al. 1999b). The pattern of results with "Gamble" (Rogers et al. 1999b), a decision making task, is more complex. Performance on the decision-making task is sensitive to damage of the OFC (but not the DLPFC), and tryptophan depletion (Rogers et al. 1999a, 1999b). However, the decision-making task elicits a slightly different deficit in fvFTD patients (Rahman et al. 1999), which is the same deficit that is seen in patients with large lesions of the frontal lobe (Manes et al. 2002) and with aneurysms of the anterior communicating artery (Mavaddat et al. 2000). The precise effect of ventral frontal lesions on decision making appears to depend on the extent and location of the lesion. As yet, no discrete lesions of frontal cortex have been found to reproduce the fvFTD deficit in decision making, nor have any pharmacological manipulations exactly mimicked it.

That tryptophan depletion impairs both reversal and decision making in normal volunteers suggests that increasing 5-HT function could improve symptoms and cognition in fvFTD. This would occur by reversing the possible deficit in 5-HT function and enhancing OFC function (Robbins 2000; Rogers and Robbins 2001). Since one of the effects of fvFTD is the same as that seen with tryptophan depletion, and decreased 5-HT binding has been found in the brains of fvFTD patients, we hypothesized that enhanced 5-HT release by chronic treatment with paroxetine would reduce the cognitive deficits. Specifically, it was hypothesized that paroxetine would improve performance of those tests that are impaired by tryptophan depletion, namely decision making (Rogers et al. 1999b), reversal learning (Rogers et al. 1999a), delayed pattern recognition (Rubinsztein et al. 2001) and paired associates learning (Park et al. 1994).

Whilst Alzheimer's disease research has yielded a variety of therapeutic strategies (Grundman et al. 1998), comparatively little work has been done on the treatment of FTD. In two recent preliminary studies, Swartz et al. (1997) assessed the effect of three different SSRIs on a group of frontal and temporal variant patients, and Moretti et al. (2003) compared the effect of paroxetine with that of a γ-amino butyric acid (GABA) analogue, piracetam. Both studies reported improvements in clinical symptoms after treatment with SSRIs. These findings are far from conclusive. Swartz et al. reported no statistically significant improvement; Moretti et al. observed significant improvement relative to the other therapy. Neither study used a placebo control. Therefore, the present placebo-controlled study assessed the effect of paroxetine therapy in patients with fvFTD to test the prediction that increasing 5-HT function would be associated with improved performance on tests of ventral frontal lobe function.

Methods

Participants

Patients with a clinical diagnosis of fvFTD were recruited through the Memory and Early Onset Dementia Clinic at Addenbrooke's Hospital, Cambridge. Patients were screened for psychiatric or neurological illness and any serious medical conditions other than FTD. All patients met internationally agreed criteria for FTD (Neary et al. 1998) and conformed to local guidelines previously applied showing at least 5 of 12 clinical features (Gregory 1999; Gregory et al. 1999; Rahman et al. 1999; Bozeat et al. 2000).

Written informed consent for all procedures was obtained from both patients and caregivers. The study was approved by the Cambridge Local Research Ethics Committee (reference number LREC 99/017).

Experimental methods

Patients were assessed on neuropsychological tasks and their caregivers were asked to fill out questionnaires. Two treatment assessments were made: one when the subject was on a daily 40-mg dose of paroxetine and another when taking identical capsules containing placebo. The order in which different patients received the two treatments was randomized and counterbalanced. The two treatment periods were separated by a minimum of 5 weeks to ensure complete recovery from the effects of the drug.

Drug regimen

Caregivers were asked to be responsible for the administration of the capsules. Patients were started on a daily 20-mg dose. This dose was increased to 30 mg in week 2 and 40 mg in week 3. The patient then remained on 40 mg for 4 weeks. The dose was cautiously reduced by 10 mg each week to avoid a SSRI discontinuation syndrome (see Table 1.). The whole treatment lasted for 9 weeks. The treatment assessment was carried out in the sixth or seventh week of the regime. The experimenter, caregiver and patient were all blind to the contents of the capsule.

On every session, subjects were assessed for verbal fluency (Benton 1968), and forward and backward digit span was assessed.

Computerized neuropsychology

The tests were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the CANTAB extensions. These tests were administered using a portable Datalux 486 microcomputer fitted with a touch sensitive screen or an Advantech PPI 120-T touchscreen. Subjects were seated comfortably ~0.5 m

Table 1 Drug regimen

Week	Daily dose of paroxetine (mg)
1	20
2	30
3	40
4	40
5	40
6	40
7	30
8	20
9	10

away from the touch screen. In order to introduce subjects to the apparatus, they were initially given a 'motor screening task' in which they were asked to respond to a series of ten flashing crosses presented at varying locations on the monitor screen by touching the center of the cross with the index finger of their preferred hand. The experimenter demonstrated by touching three crosses. After completion of this task, subjects were given the following tasks in the order described below.

Immediate and delayed pattern recognition

In the pattern recognition task, subjects are presented with 12 abstract colored patterns and asked to try to remember them. In the recognition phase, the same patterns (each paired with a novel pattern) are presented in the reverse order and subjects were asked to respond by touching the pattern they had already seen (Sahakian et al. 1988). This procedure is then repeated with 12 new patterns. The recognition phases are then repeated 20 min later to assess delayed pattern recognition.

Spatial recognition

In the spatial recognition task (Sahakian et al. 1988), five squares are presented sequentially in the different locations around the screen. In the recognition phase, subjects are presented with a choice of two squares in different locations around the screen, one of which is novel. Subjects are asked to touch the square which is in the location that a square has previously appeared in. This procedure is repeated a further three times.

Spatial span

Each trial begins with nine white boxes presented in fixed locations on the monitor screen. Initially, two of the boxes change color, one after the other in a predetermined sequence. The end of the sequence is indicated by a tone. Subjects are then asked to point to the boxes in the order in which they have changed color. After successful completion of a sequence, the number of boxes changing color increases by one, up to a maximum of nine. The test is terminated when three consecutive failures occur at any one sequence length. During each trial, the number in the bottom left corner of the screen indicated the length of the current sequence. The spatial span is calculated as the highest level at which a subject successfully recalled at least one sequence of boxes (Owen et al. 1990). This measure is used to assess the ability of subjects to hold information on-line in order to plan a series of moves such as the spatial working memory task.

Spatial working memory

In this task, subjects are required to search through a number of colored boxes on the monitor screen (by touching each one) in order to find blue tokens, which are hidden inside (Owen et al. 1990). On any trial, only a single token is hidden in one of the boxes. Once found, the next token is hidden. The key instruction is that once a token is found within a particular box, then that box will not be used again to hide a token. Two types of error are possible. First, a subject may return to a box in which a token has already been found (a between-search error). Second, a subject may return to a box already opened and shown to empty in the same trial (a within-search error). There are four trials with each of four, six and eight boxes. The task is scored according to the number of between- and within-search errors at each level of difficulty and for the use of an effective search strategy (Owen et al. 1990). Both error scores are a measure of spatial working memory, but the between-search error is more stringent as the subject is required to remember across searches which boxes contained blue tokens while conducting a new search (Joyce and Robbins 1991).

Visual discrimination learning/attentional set shifting

This visual discrimination learning/attentional set-shifting test (Downes et al. 1989) is one of attentional set shifting based in part on the Wisconsin Card Sort Test (WCST) (Milner 1964). There are nine stages in which a subject has to learn a visual discrimination to criterion (six consecutive trials correct). After reaching criterion, the subject passes to the next stage. The task starts with a simple discrimination and its reversal for stimuli varying in just one dimension (e.g. two different white line configurations). A second alternative dimension is then introduced (purple-filled shapes) and compound discrimination and its reversal are tested. To succeed, subjects must continue to respond to the previously relevant dimension whilst ignoring the presence of the new, irrelevant dimension. At the intradimensional shift stage, novel exemplars of each of the two dimensions are introduced and subjects must continue to respond to one of the two exemplars from the previously relevant dimension. Following another reversal, the extradimensional shift and its reversal are presented, again using novel exemplars of each stimulus dimension. In order to succeed at the extradimensional shift stage, the subject must shift 'attentional' or 'response' set to the previously irrelevant stimulus dimension whilst ignoring the previously relevant stimulus dimension. The extradimensional shift stage is akin to a change in category in the WCST. For each stage of the test, the computer calculates the number of trials to criterion, number of errors made, and the latency to complete each discrimination.

Decision-making 'Gamble' (Rogers et al. 1999a)

This decision-making task was based on the Iowa gambling task (Bechara et al. 1999). The subject is told that the computer has hidden at random a yellow token inside one of the ten red or blue boxes arrayed at the top of the screen. The likelihood of each choice being correct is therefore indicated to the subject on each trial by the ratio of red to blue boxes displayed on each trial. This produces a range of situations from one in which one outcome is much more likely (9:1) to those in which the two outcomes are almost equally likely (6:4). The subject is then asked whether the token is hidden in a red or a blue box. After making this initial choice, the subject attempts to increase a total points score by placing a bet on this choice being correct. The available bets appear in sequence, one after another. The subject performs the task in two separate conditions. In the ascending condition, the first bet offered is small and increases in size. In order to make a large bet, the subject has to wait until the computer displays it. The three principal measures in this task are (i) the quality of decision making, i.e., what proportion of the time the subjects indicate that the token is in the color of box that it is the most likely to be in (ii) risk taking, i.e., the percentage of points the subject is prepared to bet on the token being in the color of box they said it was and (iii) the speed of decision making, i.e., how long it takes the subject to decide which color of box is hiding the token.

Table 2 Details of the ten subjects that participated in the trial

Patient	Age (years)	Sex	National adult reading test estimated IQ	Mini mental state examination	Behavioral measures	Neuropsychological measures
1	65	Male	110	28	3	3
2	54	Male	116	29	3	3
3	75	Male	107	26	3	3
4	60	Male	97	21	3	3
5	66	Male	113	27	3	3
6	73	Male	109	28	3	3
7	75	Male	118	17	x	3
8	69	Female	118	-	3	x
9	65	Female	114	18	3	x
10	61	Female	–	15	3	All bar pattern recognition memory, decision making, digit span

Paired-associates learning

In this task (Sahakian et al. 1988; Fowler et al. 1995), six white boxes appear in a circle around the screen. These open for 3 s and in a random order. Some of the boxes open to reveal one of a number of abstract color stimuli, others may be empty. A probe stimulus appears at the center after all the boxes have been opened, and the subject is required to touch the box where it has previously appeared. At first, only two stimuli are hidden. An incorrect response results in the whole cycle of stimulus presentation being repeated for a maximum of ten cycles in total. At this point, the test would terminate. Otherwise, the stimulus set size is increased from two to three to six and finally eight different stimuli (two extra boxes being added to the display on these occasions).

Caregiver interviews and questionnaires

Behavioral data were collected during caregiver interviews using the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). This instrument assesses ten behaviors, namely: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and aberrant motor behavior (including pacing rummaging and compulsions). A frequency rating (1–4) multiplied by a severity rating (1–3) produces a subscale score for each behavior and the summation of subscale scores produces the total NPI score. The NPI has shown to be valid when compared with a variety of other diagnostic approaches and to have a high inter-rater and test-retest reliability (Cummings et al. 1994).

The Cambridge Behavioral Inventory (CBI), validated through previous work by Bozeat et al. (2000) and Perry and Hodges (1999), is a questionnaire containing 81 items. As well as changes in behavior, personality and mood (disinhibition, agitation, aggression, eating/appetite, sleep motivation and stereotypic behaviors) also included are questions that probe memory, orientation and activities of daily living. Caregivers were asked to fill out one questionnaire on every test session.

Data analysis

The experimental data were analyzed using the Statistical Package for the Social Sciences Version 9.0.1 [SPSS V9.0.1] (SPSS inc. Chicago, Ill., USA). The order that the drug was received in was included as a between-subjects factor of no interest. The data shown in the figures always represent untransformed values.

Results

Subject details

Twelve subjects were initially approached to be included in the trial. Two subjects withdrew their consent before measurements could be taken on the first drug session. The clinical details from all ten subjects are shown in Table 2. Note that incomplete data were available from four subjects, two from each counterbalancing condition, who did not wish to complete the testing.

Paired-associates learning

The numbers of errors made at the six-box level of difficulty during paroxetine and placebo are shown in Fig. 1. Only four of the subjects completed the eight-box task and so these data were unavailable for analysis. Seven of the eight subjects made more errors at the six-box stage while taking paroxetine than when taking placebo; only one subject made fewer errors on paroxetine. The overall group difference neared significance (n=8) ($F_{1,6}$=5.586, P=0.056). In summary, paroxetine increased the number of errors made on the paired-associates learning task.

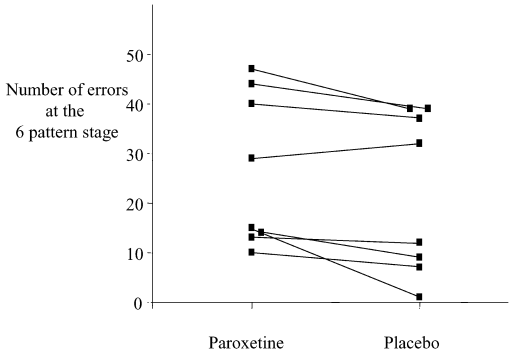

Fig. 1 Paired-associates learning: errors at the six pattern stage

Decision making

One subject was not willing to complete both arms of the test on one occasion and therefore the data from the ascend condition of the task were excluded.

Quality of decision making

There were no differences in the quality of decision making across the two different sessions, whether considered over all ratios (n=7) ($F_{1,5}$=1.760, P=0.242) or decisions made in response to particular ratios of boxes (n=7) ($F_{3,15}$=0.720, P=0.527).

Risk taking

FvFTD subjects did not bet in a significantly different fashion on paroxetine relative to placebo overall (n=7) ($F_{1,5}$=0.011, P=0.920) or in response to specific ratios ($F_{3,15}$=0.889, P=0.469). It can be seen from Table 3 that the average percentage bet did not differ between the conditions. The subjects did not significantly adjust their bets in response to the different ratios of red and blue boxes presented to them (n=7) ($F_{3,15}$=1.378, P=0.296).

Deliberation time

The time needed to come to a decision about what color box the token was hidden behind was not affected by treatment (n=7) ($F_{1,5}$=0.878, P=0.392) or in response to the different ratios of red and blue boxes (n=7) ($F_{3,15}$= 0.863, P=0.451).

In summary, there was no effect of paroxetine on any of the measures in the decision-making task.

Table 3 Means (standard errors) of psychological measures under paroxetine and placebo

	Paroxetine	Placebo
Paired-associates learning		
6 Pattern errors	13 (1.1)	7.3 (2.3)
Gamble (descend condition only)		
Quality of decision making	0.92 (0.05)	0.89 (0.09)
Percentage bet	78 (4.3)	78 (5.4)
Deliberation time (ms)	8.8 (3.0)	6.5 (1.4)
Intradimensional/extradimensional set shifting		
Intradimensional proportion correct	0.65 (0.15)	0.74 (0.12)
Extradimensional proportion correct	0.32 (0.11)	0.52 (0.09)
Reversal proportion correct	0.55 (0.07)	0.64 (0.07)
Delayed pattern recognition		
Number correct (out of 24)	13.6 (1.1)	16.2 (1.1)*
Latency (ms)	4.1 (0.7)	4.1 (0.4)
Immediate pattern recognition		
Number correct (out of 24)	15.0 (1.4)	16.7 (1.6)
Latency (ms)	5.2 (1.1)	3.7 (0.4)
Spatial span		
Span	4.1 (0.4)	4.6 (0.4)
Errors	10.3 (1.2)	12.3 (1.4)
Spatial recognition		
Latency (ms)	4.9 (0.8)	4.1 (0.5)
Percentage correct	55 (5)	64 (6)
Spatial working memory		
Between-search errors	49.9 (9.3)	49.8 (10.3)
Within-search errors	6.1 (3.5)	5.0 (2.7)
Strategy	37.8 (1.6)	36.8 (1.3)
Neuropsychiatric inventory		
NPI-12	32.4 (7.2)	28.8 (4.8)
NPI-4	15.3 (3.3)	15.5 (3.86)
Cambridge behavioral inventory	41.1 (3.6)	38.5 (4.3)
Verbal fluency	5.4 (1.7)	4.9 (1.2)
Digit span		
Forwards	5.1 (0.9)	6.3 (0.9)
Backwards	3.8 (1.2)	4.8 (1.0)

Visual discrimination learning/attentional set shifting

Rahman et al. (1999) used 'number of errors' as an assay of performance. This measure discriminated between patient and controls at reversal stages. Given that many of the subjects in the present study did not complete the extradimensional shift stage, this would not be an appropriate measure here. Instead, performance was measured by the percentage of trials in each stage that received a correct response; in this way a subject who failed to reach a given stage was scored with a zero for that stage. This pattern was investigated by using an ANOVA on the transformed proportion correct scores. The proportion scores were arcsine transformed [2 arcsine ($\sqrt{x}$)].

There was no overall effect of paroxetine (n=8) ($F_{1,6}$=2.052, P=0.202) and a similar decline in performance over the stages of the task ($F_{8,48}$=9.780, P<0.001). There was, however, a significant interaction of session by stage ($F_{8,48}$=3.446, P=0.003), indicating that paroxetine was having specific effects on particular stages. To investigate this effect further, we compared the transformed proportion correct scores for the intra-dimensional shift stage, the extra-dimensional shift stage and the combined proportion correct for the four reversal stages in three different repeated-measures ANOVAs. Paroxetine did not significantly affect the ability of the subjects to perform an intra-dimensional shift ($F_{1,6}$=0.574, P=0.477) or an extra-dimensional shift ($F_{1,6}$=4.776, P=0.072), but paroxetine tended to impair a subject's ability to perform a reversal shift ($F_{1,6}$=5.960, P=0.050) (see Fig. 2). In summary, paroxetine impaired reversal shifts on the attentional set-shifting task.

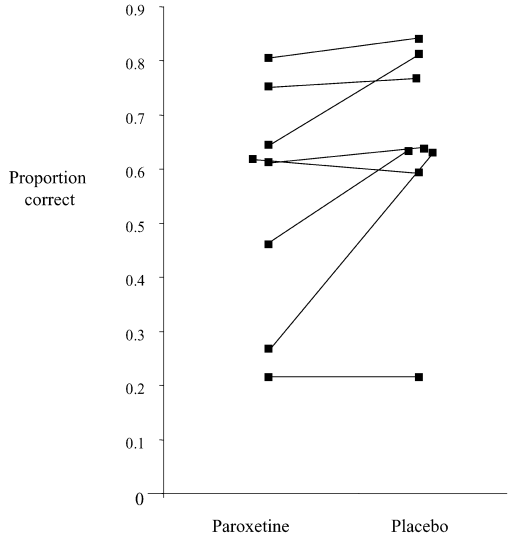

Fig. 2 Visual discrimination/attentional set shifting: proportion of correct reversal trials

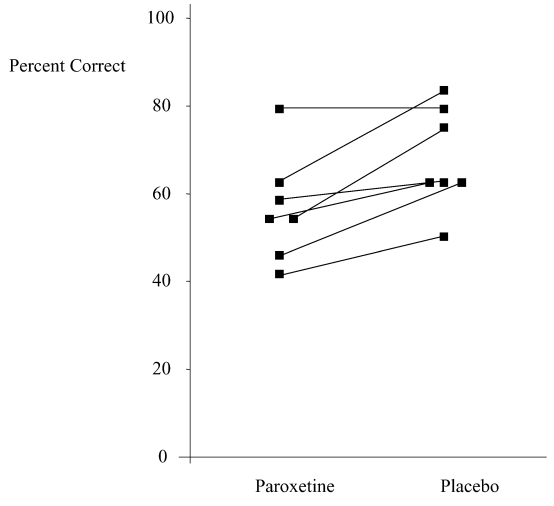

Fig. 3 Delayed pattern recognition: accuracy

Delayed pattern recognition memory

Subjects were significantly less accurate under the influence of paroxetine than placebo (n=7) ($F_{1,5}$=11.2, P=0.020). As can be seen from Fig. 3, one subject scored the same when taking paroxetine as he did when taking placebo, but the other six subjects all performed more poorly when taking paroxetine. There were no significant differences in latency (n=7) ($F_{1,5}$=0.024, P=0.884). In summary, paroxetine impaired accuracy but not speed on the delayed pattern recognition task.

Immediate pattern recognition memory

The deficit in pattern recognition after a delay was not seen if subjects were asked to recognize patterns immediately, neither in terms of accuracy (n=7) ($F_{1,5}$=0.68, P=0.45) nor latency (n=7) ($F_{1,5}$=2.429, P=0.180).

Spatial span length and errors

There was no effect of paroxetine on span length (n=8) ($F_{1,6}$=3.429, P=0.114) or on the number of errors made (n=8) ($F_{1,6}$=1.391, P=0.283).

Spatial recognition memory and response latency

Paroxetine did not have a significant impact on spatial recognition memory (n=8) ($F_{1,6}$=4.592, P=0.076) or on the transformed response latency (n=8) ($F_{1,6}$=0.594, P=0.470).

Spatial working memory

Between search errors

There was no effect of paroxetine on the number of between-search errors (n=8) ($F_{1,6}$=0.001, P=0.978). Not surprisingly, the number of between-search errors increased with increasing level of difficulty from four to six to eight box problems (n=8) ($F_{2,10}$=90.435, P<0.001). There was no interaction of difficulty with session on the number of between-search errors ($F_{2,10}$=0.125, P=0.841).

Within-search errors

ANOVA was used to compare the test session across the level of order and the three levels of search difficulty. There was no effect on the number of within-search errors found by comparing the drug and placebo conditions (n=8) ($F_{1,6}$=0.164, P=0.700). Subjects in our study did not make more within-search errors with increasing level of difficulty from four to six to eight box problems (n=8) ($F_{2,12}$=2.798, P=0.101). There was no interaction of difficulty with session on the number of within-search errors ($F_{1,7}$=0.100, P=0.784).

Strategy

The strategy scores are very consistent between paroxetine and placebo sessions ($F_{1,6}$=3.097, P=0.129).

Neuropsychiatric inventory

The NPI assesses 12 behavioral domains based on an interview with the caregiver. As well as the total NPI-12 score we also used a preselected subscore consisting of four symptoms that are particularly prominent in fvFTD (disinhibition, apathy, aberrant motor behavior and euphoria) (Levy et al. 1996). The technique of selecting a cluster of NPI scores was used after a study that used a similar method—four items that mark out Lewy body dementia (McKeith et al. 2000).

Total NPI score

Nine caregivers were willing to be interviewed on both drug conditions. There was no significant effect of paroxetine relative to placebo on the total NPI score (n=9) ($F_{1,7}$=0.119, P=0.740).

NPI4

There was no significant effect of paroxetine relative to placebo on the NPI-4 score ($F_{1,7}$=0.013, P=0.913). It can be seen from Table 3 that both the NPI4 and the total NPI did not change a great deal after treatment with paroxetine.

Cambridge Behavioral Inventory

The CBI was filled in by the caregivers on day of the interview with the subject or the days preceding it. There was no difference in the scores when the subjects were taking paroxetine relative to when the subjects were taking placebo (n=9) ($F_{1,7}$=2.25, P=0.177).

Verbal fluency and digit span

There was no effect of paroxetine relative to placebo on verbal fluency (n=7) ($F_{1,5}$=0.220, P=0.659) or forward or backward digit span ($F_{1,6}$=1.568, P=0.266; $F_{1,5}$=1.149, P=0.333).

Discussion

Paroxetine did not significantly improve scores on any of the subjective measures taken. Despite using two methods of recording caregiver's assessment of the patient (the NPI is completed during an interview with the caregiver by the interviewer and the CBI is a questionnaire filled in by the caregiver), no improvements were seen. The NPI is well validated for assessment of psychiatric symptoms in dementia, including those particularly prevalent in fvFTD such as disinhibition. Even when subscores specific to fvFTD were considered, neither trends nor significant differences were observed. These results conflict with the generally positive results from recent studies (Swartz et al. 1997; Moretti et al. 2003); Swartz et al. treated 11 patients with FTD; over half were reported to have improvements in behavioral symptoms such as disinhibition, depressive symptoms, carbohydrate cravings and compulsions.

The discrepancy between our results and those of Swartz et al. (1997) and Moretti et al. (2003) could be accounted for by a variety of factors: some patients with advanced FTD may have severe depletion of the 5-HT receptor-containing neurons, removing the substrate for paroxetine's effects. If so, it is possible that SSRIs may only be useful early in the course of this dementia. Moretti et al. (2003) used a somewhat smaller maximum dose of paroxetine (20 mg compared with 40 mg). It is conceivable that a lower dose of paroxetine could give the optimal balance between therapeutic and side effects. The discrepancy could also be due to procedural differences; as in previous studies, raters and patients were aware of the treatment, with no placebo control. Our study included a placebo control; and the patient, caregiver and experimenter were all blind to the order of treatment conditions.

Despite the lack of effect of paroxetine on subjective ratings, paroxetine did produce effects on performance on a variety of neuropsychological tests: the reversal component of the visual discrimination task, the errors in the paired-associates learning task and delayed pattern recognition memory. Paroxetine did not, however, improve performance in these tasks; in fact the effect was to increase the number of errors made (an increase in error rates on cognitive tests after paroxetine therapy was also reported by Moretti et al. 2003). These three tasks have been previously shown to be sensitive to another serotonergic manipulation, namely tryptophan depletion (Park et al. 1994; Rogers et al. 1999a, 1999b; Rubinsztein et al. 2001). Spatial recognition memory, spatial working memory and immediate pattern recognition were not significantly affected by paroxetine therapy, although some non-significant trends toward impairment were observed in the ED-shift and spatial recognition memory tasks. The tasks not significantly affected have also been shown to be relatively insensitive to tryptophan depletion (Park et al. 1994). There was only one task sensitive to tryptophan depletion (Rogers et al. 1999b), which was not affected in the same way by paroxetine—the decision-making task. The small number of subjects involved in the neuropsychological arm of this study may have limited the power to detect changes in the quality of decision making, although there was sufficient power to detect changes in the other tests. Other than the lack of effect of paroxetine on the quality of decision making, the general pattern of deficits is strikingly similar to those seen after tryptophan depletion and does not mimic the pattern of deficits shown in other psychopharmacological manipulations, for example: methylphenidate (Elliott et al. 1997; Rogers et al. 1999a).

It is generally assumed that chronically administered SSRIs cause an increase in releasable pools of 5-HT through reuptake inhibition and desensitization of 5-HT autoreceptors, (although this has recently been challenged on the basis of microdialysis studies in the macaque (Smith et al. 2000). While it is possible that any interference with the serotonergic system would disrupt performance on these tasks, if a chronic course of paroxetine increased 5-HT, it would generally have effects opposite to those seen in tryptophan depletion. However, it could be that the course of paroxetine given was not long enough for the desensitization to be complete in those areas of the frontal lobe that have been particularly implicated in reversal learning and delayed pattern recognition.

Since it has been suggested that the OFC is critically involved in both reversal learning and delayed pattern recognition (Rogers et al. 1999a; Rubinsztein et al. 2001) and that this is assumed to be a key site of dysfunction in fvFTD (Rahman et al. 1999), it is important to attempt to understand the changes effected by paroxetine in this area. Blier and de Montigny (1998) found that the evoked release of tritiated 5-HT in the guinea pig was significantly enhanced in the OFC after an 8-week course of high-dose paroxetine or fluoxetine but not after 3 weeks. Although a 4- to 6-week study period is conventional for testing the efficacy of a treatment for depression, 8–12 weeks is typically used in assessment of SSRI treatment of obsessive–compulsive disorder (Montgomery 1996). It is possible that a longer course of paroxetine could produce different results on neuropsychological measures and perhaps even subjective measures.

The difficulties in understanding the potential changes in the serotonergic system in different parts of the brains of our subjects after a 6-week course of paroxetine are further complicated by the fact that serotonergic function is disrupted in FTD. It is therefore of interest to know whether similar effects would be observed in normal individuals after a similar course of paroxetine. It is possible that paroxetine is unable to exert an effect on the damaged OFC, and that serotonergic influences on the striatum or other serotonergically innervated regions connected to the OFC produce the changes observed.

In summary, the data from this study offer no evidence to support the use of paroxetine as a treatment for fvFTD. Paroxetine treatment did not affect abnormal behaviors as rated by caregivers and caused a decrease in accuracy in paired-associates learning, reversal learning and delayed pattern recognition. The pattern of deficits of subjects with fvFTD after a 6-week course of paroxetine closely resembles the pattern of deficits observed in normal individuals who have undergone tryptophan depletion.

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References

Bechara A, Damasio H, Damasio AR, Lee GP (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 19:5473–5481

Benton AL (1968) Differential behavioural effects in frontal lobe disease. Neuropsychologia 6:53–60

Blier P, de Montigny C (1998) Possible serotonergic mechanisms underlying the antidepressant and anti-obsessive-compulsive disorder responses. Biol Psychiatry 44:313–323

Blier P, de Montigny C (1999) Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. Neuropsychopharmacology 21:91S–98S

Bozeat S, Gregory CA, Ralph MA, Hodges JR (2000) Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 69:178–186

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314

Dolan M, Anderson IM, Deakin JF (2001) Relationship between 5-HT function and impulsivity and aggression in male offenders with personality disorders. Br J Psychiatry 178:352–359

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW (1989) Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 27:1329–1343

Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW (1997) Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology 131:196–206

Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ (1995) Computerized delayed matching to sample and paired associate performance in the early detection of dementia. Appl Neuropsychol 2:72–78

Gregory CA (1999) Frontal variant of frontotemporal dementia: a cross-sectional and longitudinal study of neuropsychiatric features. Psychol Med 29:1205–1217

Gregory CA, Serra-Mestres J, Hodges JR (1999) Early diagnosis of the frontal variant of frontotemporal dementia: how sensitive are standard neuroimaging and neuropsychologic tests? Neuropsychiatry Neuropsychol Behav Neurol 12:128–135

Grundman M, Corey-Bloom J, Thal LJ (1998) Perspectives in clinical Alzheimer's disease research and the development of antidementia drugs. J Neural Transm Suppl 53:255–275

Hodges JR, Miller B (2001) The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: part I. Neurocase 7:31–35

Joyce EM, Robbins TW (1991) Frontal lobe function in Korsakoff and non-Korsakoff alcoholics: planning and spatial working memory. Neuropsychologia 29:709–723

Levy ML, Miller BL, Cummings JL, Fairbanks LA, Craig A (1996) Alzheimer disease and frontotemporal dementias. Behavioral distinctions. Arch Neurol 53:687–690

Manes F, Sahakian B, Clark L, Rogers R, Aitken M, Robbins T (2002) Decision-making processes following damage to the prefrontal cortex. Brain 125:624–639

Mann JJ (1999) Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. Neuropsychopharmacology 21:99S–105S

Mavaddat N, Kirkpatrick PJ, Rogers RD, Sahakian BJ (2000) Deficits in decision-making in patients with aneurysms of the anterior communicating artery. Brain 123:2109–2117

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R (2000) Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 356:2031–2036

Milner B (1964) Effects of different brain lesions on card sorting. Arch Neurol 9:100–110

Montgomery SA (1996) Long-term management of obsessive-compulsive disorder. Int Clin Psychopharmacol 11[Suppl 5]:23–29

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A (2003) Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. A randomized, controlled, open 14-month study. Eur Neurol 49:13–19

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554

Neary D, Snowden JS, Mann DM (2000) Classification and description of frontotemporal dementias. Ann New York Acad Sci 920:46–51

Orrell MW, Sahakian BJ (1991) Dementia of frontal lobe type (editorial). Psychol Med 21:553–556

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 28:1021–1034

Park SB, Coull JT, McShane RH, Young AH, Sahakian BJ, Robbins TW, Cowen PJ (1994) Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. Neuropharmacology 33:575–588

Perry RJ, Hodges JR (1999) Attention and executive deficits in Alzheimer's disease. A critical review. Brain 122:383–404

Plaisted KC, Sahakian BJ (1997) Dementia of the frontal lobe type-living in the here and now. Aging Mental Health 1:293–295

Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW (1999) Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 122:1469–1493

Ratnavalli E, Brayne C, Dawson K, Hodges JR (2002) The prevalence of frontotemporal dementia. Neurology 58:1615–1621

Robbins TW (2000) Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp Brain Res 133:130–138

Rogers RD, Robbins TW (2001) Investigating the neurocognitive deficits associated with chronic drug misuse. Curr Opin Neurobiol 11:250–257

Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, Hopwood A, Wallace C, Deakin JF, Sahakian BJ, Robbins TW (1999a) Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology 146:482–491

Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JF, Sahakian BJ, Robbins TW (1999b) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20:322–339

Rubinsztein JS, Rogers RD, Riedel WJ, Mehta MA, Robbins TW, Sahakian BJ (2001) Acute dietary tryptophan depletion impairs maintenance of "affective set" and delayed visual recognition in healthy volunteers. Psychopharmacology 154:319–326

Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, Robbins TW (1988) A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 111:695–718

Smith TD, Kuczenski R, George-Friedman K, Malley JD, Foote SL (2000) In vivo microdialysis assessment of extracellular serotonin and dopamine levels in awake monkeys during sustained fluoxetine administration. Synapse 38:460–470

Sparks DL, Markesbery WR (1991) Altered serotonergic and cholinergic synaptic markers in Pick's disease. Arch Neurol 48:796–799

Swartz JR, Miller BL, Lesser IM, Darby AL (1997) Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. J Clin Psychiatry 58:212–216