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Neural correlates of adjunctive rivastigmine treatment to antipsychotics in schizophrenia: A randomized, placebo-controlled, double-blind fMRI study

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Facilitation of central cholinergic activity may form a potential treatment strategy for cognitive impairment in schizophrenia. In a randomized, placebo-controlled, double-blind, parallel-group design, we investigated the neural correlates of cognitive effects of rivastigmine, an acetylcholinesterase inhibitor, given as an add-on therapy to antipsychotic-treated schizophrenia patients. Thirty-six chronic schizophrenia patients with mild cognitive impairment took part. After 1 week on placebo (baseline), all patients entered a double-blind protocol; 18 were allocated to receive rivastigmine and 18 placebo for the next 12 weeks (final sample with usable imaging data: 11 patients on rivastigmine, 10 on placebo). All patients underwent functional magnetic resonance imaging during a parametric '*n*-back' task, involving monitoring of dots in particular locations on a screen at a given delay from the original occurrence, twice: at baseline and 12 weeks post-rivastigmine/placebo treatment. Compared to placebo, rivastigmine produced only a small and non-significant improvement in task accuracy across all conditions with no change in response latency, and increased activity in the extrastriate visual cortex in areas associated with visual and spatial attention but not in any region within the working memory network. Our observations suggest that cholinergic enhancement with rivastigmine at doses known to be effective in Alzheimer's disease does not produce strong and clinically meaningful cognitive and neural changes in schizophrenia patients treated with atypical antipsychotics although the neural effects in terms of enhanced neuronal activity in regions associated with visual and spatial attention are consistent with those reported previously with cholinergic enhancement in healthy subjects.

Introduction

Individuals with schizophrenia display multifaceted cognitive impairment (review, Rund, 1998) regardless of a change in their symptom state (Hughes et al., 2003). The level of cognitive impairment is found to predict the functional outcome of the illness more strongly than the severity of positive or negative symptoms (Green, 1996; Velligan et al., 1997; Addington and Addington, 1999; Evans et al., 2003). An urgent need, therefore, has been felt in recent years to find novel treatment approaches specifically targeting cognitive deficits in this population (Sharma and Harvey, 2000; Harvey et al., 2004). One suggested approach has been to use acetylcholinesterase inhibitors (AChE-Is) (Friedman et al., 1999), which is currently the main therapeutic approach to treat cognitive decline in Alzheimer's disease (AD; reviews Doody, 2003; Giacobini, 2003; Terry and Buccafusco, 2003). AChE-Is, such as donepezil, tacrine, rivastigmine and galantamine, are found to improve cognitive functions in AD (reviews, Doody, 2003; Giacobini, 2003; Terry and Buccafusco, 2003; Harry and Zakzanis, 2005). The data showing an association between the decreases in choline acetyltransferase (ChAT) levels at post-mortem and the severity of antemortem cognitive deficits in schizophrenia patients (Powchik et al., 1998), taken together with observations of positive cognitive effects of cholinergic facilitation in AD patients as well as in experimental animals (e.g. Mandel et al., 1989; Decker and McGaugh, 1991), have provided justification for the extension of this approach to treat cognitive deficits in schizophrenia (Friedman et al., 1999).

There have been preliminary studies (Buchanan et al., 2003; Stryjer et al., 2002) and case reports (MacEwan et al., 2001; Risch et al., 2001; Howard et al., 2002) showing the beneficial cognitive effects of donepezil as add-on therapy in schizophrenia or schizoaffective disorder, though two randomized, double-blind, placebo-controlled studies failed to detect such an effect (Friedman et al., 2002; Tugal et al., 2004). In some studies of schizophrenia, a beneficial

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effect of donepezil has also been seen as improvement in psychotic symptoms (Stryjer et al., 2003), depression (Risch et al., 2001) and tardive dyskinesia (Caroff et al., 2001). Additionally, preliminary functional magnetic resonance imaging (fMRI) studies have shown that donepezil, compared to placebo, increases the brain's response during cognitive paradigms in the frontal (Risch et al., 2001; Nahas et al., 2003) and basal ganglia regions (Risch et al., 2001) in schizophrenia patients. Extending this line of enquiry, we examined the effects of 12-weeks rivastigmine treatment adjunctive to antipsychotics, compared to placebo, using a double-blind, within-subjects design on behavioral performance and blood oxygenation level-dependent (BOLD) regional brain activity during a parametric '*n*-back' working memory task in stable patients with chronic schizophrenia.

While most previous studies have used donepezil to augment cholinergic function, we used rivastigmine, a pseudo-irreversible, central nervous system-selective, AChE-I (Polinsky, 1998). Rivastigmine carries with it the theoretical advantage of inhibiting butyrylcholinesterase (BuChE) as well as AChE, both of which are known to be involved in cognition (Mesulam et al., 2002). It is classified as an intermediate-acting or pseudo-irreversible agent due to its long inhibition of AChE (up to 10 h), compared to tacrine and donepezil which are classified as short-acting or reversible agents (binding to AChE hydrolyzed within minutes). In AD, it has been found to produce improvements in global scales of behavior, daily activities, cognition and psychopathology, with benefits occurring as early as 12 weeks post-treatment (reviews, Birks et al., 2000; Jann, 2000; Williams et al., 2003) and to enhance brain activity in the frontal, parietal (Potkin et al., 2001; Vennerica et al., 2002) and temporal regions (Vennerica et al., 2002) across a range of cognitive tasks. More recently, rivastigmine has been reported to have precognitive effects also in patients with Parkinson's disease (Emre et al., 2004). A preliminary study has shown beneficial cognitive effects with rivastigmine in schizophrenia (Lenzi et al., 2003).

Working memory is known to activate a distributed network of areas including frontal, especially the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate, and parietal regions (Callicott et al., 1999; Kumari et al., 2003a,b). On the basis of the previous literature in AD as well as in schizophrenia, we hypothesized that rivastigmine treatment, as compared to placebo, would be accompanied by an altered BOLD response in associated network including the frontal and parietal regions found previously to be activated with the '*n*-back' task in healthy subjects (Callicott et al., 1999; Kumari et al., 2003a,b). Although the study set out to identify brain activity changes as measured by fMRI, we also recorded task-specific behavioral measures and, based on the previous observations in AD and schizophrenia, expected to see a change in the patients' clinical status and, if so, a corresponding change in activity in brain regions known to have an association with symptoms of schizophrenia, namely the DLPFC (e.g. Perlstein et al., 2001; Bertolino et al., 2003; Molina et al., 2003) and anterior cingulate (Braus et al., 2002).

Materials and methods

Subjects

The study involved 36 patients with schizophrenia diagnosed by a trained psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). All subjects received full explanation of the study prior to screening and met the following inclusion criteria: (i) aged between 18 and 55 years, (ii) receiving treatment with an atypical antipsychotic, (iii) no change in medication/dose of current medication over the last 6 weeks and unlikely to require change in antipsychotic medication, (iv) no adjunctive anticholinergic treatment, (v) negative urine screening for illicit drugs and negative pregnancy test for females, (vi) cooperative and able to ingest oral medication, and (vii) able to provide written informed consent. Because we aimed to detect improvements in cognition, only patients with evidence of pre-existing mild cognitive impairment were included based on between 1 and 2 standard deviations (SD) below expected performance on the basis of age and education level on the California Verbal Learning Test (Delis et al., 1987). Patients were excluded if they had (i) another concurrent DSM-IV diagnosis, (ii) known hypersensitivity to cholinergic agents, (ii) current treatment with benzodiazepines or antidepressants, (iii) history of neurodegenerative disorder in first degree relative, (iv) medical conditions that preclude administration of rivastigmine, (v) history of DSM-IV substance dependence in the last year or substance abuse within the last month, (vi) lifetime history of trauma resulting in loss of consciousness for 1 h or longer, (vii) participation in another investigational drug study within 6 weeks prior to study entry, (viii) recent (within last 3 months) history of suicidal or violent acts, (ix) neuroimaging contraindicated e.g. metal plates in body, and (x) current diagnosis of uncontrollable seizure disorder, active peptic ulceration, severe and unstable cardiovascular disease or/and acute severe unstable asthma.

Of 36 patients initially enrolled, 21 patients remained in the study with continued consent and provided usable fMRI data on both occasions. The reasons for the drop out were: unwillingness to continue with the study/study drug ($n = 9$; none due to side effects or adverse events), not being able to stay in the scanner on the first/second occasion ($n = 4$), unusable fMRI data ($n = 1$) or a relapse ($n = 1$; soon after the baseline). Of the final sample, 11 patients had been assigned to the rivastigmine group, and 10 patients to the placebo group (see Study design). Twelve patients were on olanzapine (6 belonging to the rivastigmine group, 6 to the placebo group), 6 patients on risperidone (2 belonging to the rivastigmine group, 4 to the placebo group) and 3 patients were on quetiapine (belonging to the rivastigmine group). Seventeen patients were regular cigarette smokers, 8 patients belonging to the rivastigmine group and 9 patients to the placebo group. Demographic, clinical and cognitive characteristics of patients are presented in Table 1.

The study procedures were approved by the ethics committee of the Institute of Psychiatry, London. All patients provided

Table 1
Demographic, clinical and cognitive characteristics of patients with schizophrenia

	Rivastigmine Mean (SD)	Placebo Mean (SD)
Age	42.55 (8.81)	44.40 (11.64)
Sex	9 men, 2 women	5 men, 5 women
Education (years)	10.09 (3.70)	11.70 (0.95)
Age at onset of psychotic symptoms	25.09 (7.94)	28.80 (10.57)
Number of previous psychiatric hospitalizations	4.22 (3.11)	5.00 (4.18)
Predicted full scale IQ (NART)	96.54 (12.86)	100.00 (12.95)
CVLT total learning scores	33.63 (9.14)	31.22 (11.70)

NART: National Adult Reading Test (Nelson and Willison, 1991); CVLT: California Verbal Learning Test (Delis et al., 1987; normative scores for 40 years aged men = 55, women = 50).

written informed consent after the study procedures had been explained.

Study design

All patients were placed on a single blind placebo for 1 week in order to counteract any motivational influence of the belief of being on a cognitive enhancer drug. After 1 week on placebo, all patients underwent (baseline) fMRI (see Cognitive activation paradigm) and clinical assessments (see Clinical assessments), and then were randomized into the double-blind protocol so that, on 1:1 basis, half of the patients received rivastigmine and the remaining half received placebo for the next 12 weeks and were reassessed on fMRI and clinical variables.

Drug dose and administration

Patients assigned to the rivastigmine group received 1.5 mg/bd dose for the first 2 weeks, 3 mg/bd over the next 2 weeks, 4.5 mg/bd dose for the next 2 weeks and then 6 mg/bd for the remaining period so at the time of second scan all patients were on the 12 mg dose. The choice and scheduling of dosages selected were based upon the cognitive effects of rivastigmine seen in AD patients. The placebo group received capsules containing ascorbic acid (100 mg).

Clinical assessments

Symptoms were rated within 4 days of scanning using the Positive and Negative Syndrome scale (PANSS) (Kay et al., 1987) on both occasions, the assessor being blind to treatment group. Side effects were also recorded within 4 days of scanning using the Simpson–Angus Rating Scale for Extrapyramidal Side Effects (Simpson and Angus, 1970), Barnes Akathisia Scale (Barnes, 1989) and the Abnormal Involuntary Movement Scale (Guy, 1976). Given the high incidence of gastrointestinal side effects upon the initiation of therapy with rivastigmine in AD patients (Rosler et al., 1999), gastrointestinal side effects were closely monitored during the first 4 weeks and then on a weekly basis throughout the study period.

Cognitive activation paradigm

We used a modified version of the '*n*-back' tasks used previously by Callicott et al. (1999) and Kumari et al. (2003a,b). It involved monitoring locations of dots (presentation time: 450 ms; inter-stimulus-interval: 1500 ms) within a diamond shaped box on the screen at a given delay from the original occurrence (0-back, 1-back or 2-back). There were three 30-s active conditions (0-back, 1-back and 2-back) in total presented to subjects five times in pseudo-random order, controlling for any order effect. In total, 15 stimuli were presented in each 30-s active block. Each active condition started with a 15-s resting baseline ('Rest' appeared on the screen during this period), and begun with a 750 ms text delay allowing the patients to notice a change in task condition. The experiment lasted 11 min and 15 s in total. Patients viewed the paradigm projected onto a screen at the end of the scanner couch via a prismatic mirror as they lay in the scanner. On-line accuracy and latency data were determined via button presses on every trial using the right thumb from all patients. Patients were required to press the button corresponding to the correct location of the 0-back (current) stimulus, 1-back (previous) stimulus or 2-back (previous but one) stimulus (chance performance equals 25%; presentation of dots totally random within all 30-s blocks).

Image acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. In each of 16 near-axial non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 225 T_2*-weighted MR images depicting blood–oxygen-level-dependent contrast (Ogawa et al., 1990) were acquired over the experiment with echo time (TE) = 40 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm and inter-slice gap = 0.7 mm. In the same session, a high resolution 3-D inversion recovery prepared spoiled GRASS volume data set was acquired with TE = 5.3 ms, TI = 300 ms, TR = 12.2 ms, in-plane resolution = 0.94 mm and slice thickness = 1.5 mm.

General procedure

Patients were told that the purpose was to investigate the brain correlates of the effects of rivastigmine on cognitive performance. They were requested to abstain from alcohol for at least 24 h prior to their scanning. All subjects practiced (once) on the task a week in advance of the scheduled scan to minimize any practice effects. After the second scan was over, all patients were asked whether they thought they had been assigned to receive rivastigmine or placebo.

Data analysis

Behavioral and clinical measures

Behavioral performance was assessed as percentage of response correct (accuracy) and the average time (in ms) taken to respond on correct responses (RT latency). The effects of rivastigmine over 0-back, 1-back and 2-back conditions were analyzed, separately for response accuracy and latency, by Drug Group (rivastigmine, placebo) × Time (baseline, 12 weeks) × Load (0-back, 1-back and 2-back) analyses of variance (ANOVA) with Drug Group as a between-subjects factor and Load and Time as within-subjects factors, followed by lower order ANOVAs and post hoc mean comparisons wherever appropriate. Effects of rivastigmine on positive symptoms, negative symptoms, general psychopathology score, total PANSS scores and various side effects measures were analyzed (separately) using Drug Group × Time ANOVA. The effect sizes were estimated using the partial Eta^2 for all observations. All analyses were performed by SPSS windows (version 11). Alpha level for testing significance of effects was $P = 0.05$ unless stated otherwise.

Functional MRI

Image pre-processing

For each subject, the 225 volume functional time series was motion corrected (Friston et al., 1996), transformed into stereotactic space, spatially smoothed with a 10 mm FWHM Gaussian filter and band pass filtered using statistical parametric mapping software (SPM99; http://www.fil.ion.ucl.ac.uk/spm).

Models and statistical inferences

Data were analyzed using a two-stage random effect procedure (Friston et al., 1999). The first stage identified patient-specific task-

related activations at baseline and 12 weeks with a factorial model consisting of three active conditions (0-back, 1-back and 2-back) and rest as an implicit baseline. The boxcar for each 30-s epoch was convolved with the hemodynamic response function. The second stage of the analysis used separate ANOVAs, thresholded at $P < 0.05$ corrected for multiple comparisons at the cluster level, for each of 0-, 1- and 2-back > rest and 1- and 2-back > 0-back contrasts. Using planned contrasts (placebo at baseline versus rivastigmine at baseline; placebo at baseline versus placebo at 12 weeks; rivastigmine at baseline versus rivastigmine at 12 weeks), the SPM ANOVAs were used to identify regions from which to extract data for more detailed statistical examination within SPSS. Extracted data were tested for Drug Group (rivastigmine, placebo) × Time (baseline, 12 weeks) interactions (the *difference* of *differences* in baseline versus 12-week comparisons under placebo and rivastigmine) in a mixed model repeated measures ANOVA. Finally, generic activations within the working memory network were identified for 0-, 1- and 2-back > rest and 1- and 2-back > 0-back contrasts using a one-sample *t* test collapsing baseline data sets for both groups (see Results).

Given the lack of hypothesized neural effects of rivastigmine treatment in the analysis with the factorial model (see Results), we further analyzed the fMRI data using a random-effects parametric model consisting of one covariate with three levels (0-, 1- and 2-back) and rest as the implicit baseline to identify group and drug effects in memory load-related activations following the procedures described earlier for the factorial model. This analysis examined whether working memory network responses were non-linear at baseline and, if so, the possibility that rivastigmine treatment may lead to appearance of, or enhanced, load-dependent linearity in activity in some or all relevant regions.

Results

Behavioral measures

There was a decrease in response accuracy with increasing working memory load in both groups on both occasions (Load, $F = 70.65$, $df = 2, 38$, $P = 0.001$; partial $\text{Eta}^2 = 0.79$; Fig. 1). The main effect of Time was not significant ($F = 3.27$, $df = 1, 19$, $P < 0.09$; partial $\text{Eta}^2 = 0.15$). Drug group × Time interaction also failed to reach significance ($F = 2.21$, $df = 1, 19$, $P = 0.15$; partial $\text{Eta}^2 = 0.10$) although the effects were in the expected direction, showing some improvement in performance in the rivastigmine group at 12 weeks ($F = 4.28$, $df = 1, 10$, $P = 0.06$; partial $\text{Eta}^2 = 0.30$) but no change in the placebo group weeks ($F = 0.07$, $df = 1, 9$, $P = 0.78$; partial $\text{Eta}^2 = 0.01$). No other main or interactive effects were significant. For response latency, there was only a significant effect of Load ($F = 6.06$, $df = 2, 38$, $P = 0.005$; partial $\text{Eta}^2 = 0.24$) with faster latencies for the 1-back than the 0-back condition (quadratic $F = 12.08$, $df = 1, 19$, $P = 0.003$) in both groups on both occasions (Fig. 1). The faster reaction times found for 1-back and 2-back compared to 0-back conditions implied that patients had prepared their response by placing their thumb on the correct button in advance of the cue to press (the presentation of the 1 or 2 forwards stimulus), a strategy not possible in the 0 back-condition where the response was defined by the cue itself (Kumari et al., 2003a,b). As for the accuracy, the Drug Group × Time interaction for the latency measure was also in the expected direction (a decrease in RT at 12 weeks under rivastigmine that was absent under placebo) but failed to reach significance. No other effects were significant for response latency (all Fs < 1).

Clinical measures

No significant Drug Group, Time or Drug Group × Time interaction effects occurred for PANSS positive or negative symptom ratings (all Ps > 0.25). PANSS general psychopathology ratings (Time: $F = 5.23$, $df = 1, 19$, $P = 0.01$; partial $\text{Eta}^2 = 0.22$) as well as the total PANSS scores (Time: $F = 5.50$, $df = 1, 19$, $P = 0.03$; partial $\text{Eta}^2 = 0.23$) were lower in both groups at 12 weeks assessments; although Drug Group × Time interactions were not significant, the data consistently showed greater improvements in the rivastigmine than the placebo group (Table 2). No significant main or interactive effects occurred for side effect ratings (Table 2). We did not observe noticeable gastrointestinal problems in the rivastigmine or the placebo group.

At the end of the two experimental sessions, five patients of the rivastigmine group believed they were receiving placebo while 4

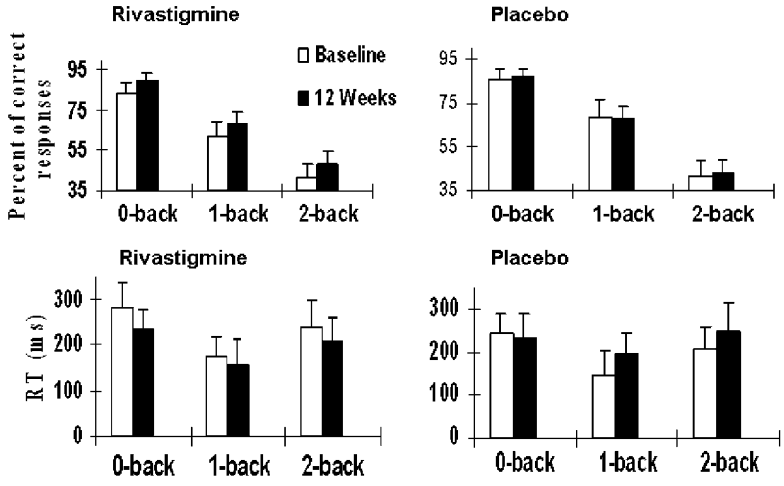

Fig. 1. Response accuracy (% correct; error bars demonstrate standard error of the mean; top panel) and latency (in ms; error bars demonstrate standard error of the mean; bottom panel) for 0-back, 1-back and 2-back trials (chance performance for accuracy equals 25%) at baseline and 12 weeks for patients allocated to the rivastigmine or placebo.

Table 2
Symptoms and side effects at baseline and 12 weeks in the rivastigmine and placebo groups

	Rivastigmine		Placebo	
	Baseline Mean (SD)	12 weeks Mean (SD)	Baseline Mean (SD)	12 weeks Mean (SD)
PANSS: positive symptom	12.09 (5.24)	9.82 (2.40)	10.50 (4.90)	9.70 (3.53)
PANSS: negative symptoms	12.00 (5.78)	9.70 (3.53)	12.80 (3.12)	11.70 (3.86)
PANSS: general psychopathology	28.09 (10.25)	23.00 (6.00)	30.90 (6.76)	27.30 (5.21)
PANSS: total score	52.45 (20.83)	43.37 (11.60)	54.50 (11.05)	48.70 (9.78)
SAS score	1.36 (2.34)	0.72 (1.01)	1.70 (1.57)	0.80 (0.63)
BAS score	1.27 (2.87)	0.36 (0.92)	2.10 (2.89)	1.90 (2.28)
AIMS score	1.09 (2.77)	0.36 (0.81)	0.60 (0.70)	0 (0)

PANSS: Positive and Negative Syndrome Scale.
SAS: Simpson–Angus Rating Scale for Extrapyramidal Side Effects.
BAS: Barnes Akathisia Scale.
AIMS: Abnormal Involuntary Movement Scale.

patients of the placebo group believed they were receiving the active drug, rivastigmine.

Functional MRI

Our SPM factorial ANOVA analysis revealed no significant difference at $P < 0.05$ corrected at the cluster level at baseline between the rivastigmine and placebo groups in any task-related activations. At the same threshold, rivastigmine treatment was associated with a relative increase in response (12 week rivastigmine > baseline rivastigmine) in the right middle occipital gyrus during 1-back > rest, 2-back > rest, and 1-back > 0-back contrasts, and bilaterally in this region for the 2-back > 0-back contrast (Table 3, Figs. 2a–d). The same region did not show differential activation under placebo. To examine whether this apparent difference between the Groups was significant, data were extracted from the region and tested in a repeated measures mixed model ANOVA within SPSS to confirm a significant Drug Group × Time interaction (greater increase at 12 weeks from baseline under rivastigmine than placebo) (1-back > rest: $F = 7.22$, $df = 1, 19$, $P = 0.01$; 2-back > rest: $F = 3.82$, $P = 0.07$; 1-back > 0-back: $F = 11.03$, $P = 0.004$; 2-back > 0-back: right hemisphere, $F = 7.84$, $P = 0.01$; left hemisphere, $F = 4.84$, $P = 0.04$) (Figs. 2a–d). No region was found showing the opposite effect (greater increase at 12 weeks from baseline under placebo than rivastigmine) other than the right superior frontal gyrus during the 0-back > rest contrast (Drug Group × Time: $F = 5.66$, $df = 1, 19$, $P = 0.03$). No regions showed a significant decrease at 12 weeks compared to baseline under rivastigmine or placebo in the SPM ANOVA (12-week rivastigmine < baseline rivastigmine; 12-week placebo < baseline placebo).

Table 3
Brain regions showing increases in activity at 12 weeks over baseline ($P < 0.05$, corrected at the cluster level unless indicated otherwise) with rivastigmine or placebo treatment

Contrast	BA	Hemisphere	x	y	z	P
			(in mm)			
Rivastigmine 12 weeks > Baseline						
0-back > rest			None			
1-back > rest						
Middle Occipital Gyrus	19	Right	40	−70	18	*0.044
2-back > rest						
Middle Occipital Gyrus	19	Right	46	−66	4	0.028
1-back > 0-back						
Middle Occipital Gyrus	19	Right	42	−72	18	0.02
2-back > 0-back						
Middle Occipital Gyrus	19	Right	46	−66	10	0.001
	18/19	Left	−14	−82	14	0.001
Placebo 12 weeks > Baseline						
0-back > rest						
Superior Frontal Gyrus	9	Right	28	30	36	0.003
1-back > rest						
2-back > rest		None				
1-back > 0-back						
2-back > 0-back						

No region showed a significant decrease in activity from baseline to 12 weeks with either treatment.
BA = Brodmann area.

Given the previous reports of an influence of cholinergic augmentation on the working memory network in normal subjects, we looked specifically for changes (either increases or decreases) within the network using the SPM ANOVAs. We found no evidence of increases in activity (contrast: 12 week rivastigmine > baseline rivastigmine) or decreases in activity (contrast: baseline rivastigmine > 12 week rivastigmine) in the anterior cingulate, superior parietal, superior frontal or DLPFC regions, even at the lowest acceptable threshold of $P < 0.05$ uncorrected. Since previous studies have shown normalizing effects of atypical antipsychotic treatment in frontal regions (Honey et al., 1999; Braus et al., 2001, 2002; Mendrek et al., 2004), we examined task activation for the combined group of patients at baseline. Depending on the working memory load, the generic network of regions identified, as expected, included bilateral activations in the superior frontal gyrus, the superior parietal lobe, the anterior cingulate gyrus, unilateral activation in the left sensorimotor cortex (corresponding to the right hand button press) and, most importantly with respect to previous results, the right DLPFC (Table 4, Fig. 3).

The analysis with the parametric model showed no difference between the placebo and rivastigmine groups at baseline. Across all patients, the right DLPFC ($x = 36$, $y = 36$, $z = 16$; $t = 7.86$), right anterior cingulate ($x = 4$, $y = 24$, $z = 42$; $t = 7.84$), bilateral superior frontal gyrus (left: $x = -42$, $y = 4$, $z = 40$, $t = 5.91$; right: $x = 50$, $y = 10$, $z = 18$; $t = 7.08$) and bilateral inferior/superior parietal cortex (left: $x = -48$, $y = -48$, $z = 40$; $t = 5.50$; right: $x = 40$, $y = -60$, $z = 48$; $t = 7.53$) showed linear load-dependent

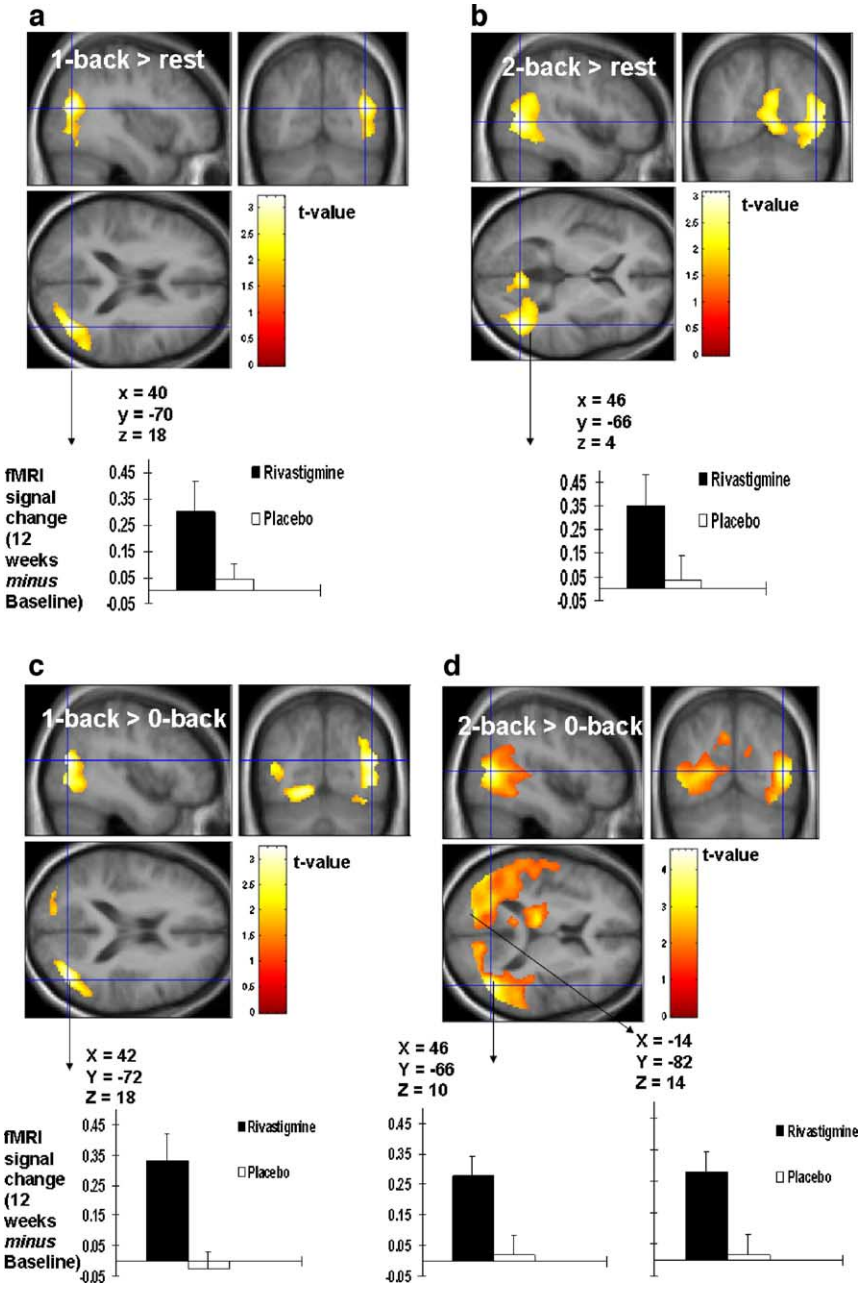

Fig. 2. Significant increases in fMRI activity at 12 weeks over baseline with rivastigmine treatment in the middle occipital gyrus during the 1-back and 2-back versus rest (a–b), and 1-back and 2-back versus 0-back contrasts (c–d) (threshold $P < 0.05$; cluster-level correct). Left hemisphere is shown on the left of the coronal view.

increases in activity at baseline. There was no significant effect of rivastigmine in any of these regions, as shown earlier in the analyses using the factorial model.

Discussion

The present study was designed to assess the neural mechanisms underlying the effects of rivastigmine treatment in cognitive functions, particularly attention and working memory, in patients with schizophrenia using a rigorous double-blinded parallel-group design and varying levels of task difficulty. We found no significant change in clinical or behavioral measures and no support for our hypotheses of enhanced activity in working memory neural network although there was striking similarity in the fMRI results showing enhanced visual cortex activity (outside the working memory network) with rivastigmine treatment in patients with schizophrenia presented here and those reported with cholinergic enhancement in previous studies of healthy subjects as discussed further.

Behavioral and clinical findings

The effects of rivastigmine on behavioral measures were not significant. Although the effects on accuracy measure on all active conditions, including the 0-back condition with no working

Table 4
Brain regions with significant increases (a) and decreases (b) in task-related activity ($P < 0.05$; corrected at the voxel level) across all patients at baseline

Brain region	BA	Left (in mm)			*t* value	Right (in mm)			*t* value
		x	*y*	*z*		*x*	*y*	*z*	
a: Increases									
0-back > rest									
Anterior cingulate	32	−2	4	48	10.21				
	6	−2	4	56	9.86				
Sensorimotor cortex	4	−40	−32	48	9.41				
	2	−52	−28	44	9.25				
Superior parietal lobe	7	−28	−58	56	8.95				
1-back > rest									
Anterior cingulate	32	0	8	46	8.32				
	6	0	4	56	9.34				
Superior frontal gyrus	6					38	6	50	6.45
Sensorimotor cortex	4	−56	−28	46	9.55				
	4/6	−30	−4	56	9.41				
Superior parietal lobe	40	−50	−38	52	9.19	32	−54	54	6.85
	40					52	−38	42	6.51
	7					12	−58	52	6.30
2-back > rest									
Anterior cingulate	32	−4	4	56	10.09				
Inferior frontal gyrus	44	−48	10	26	7.56	52	10	24	7.06
Superior frontal gyrus	6	−32	−2	44	9.30	36	6	48	7.53
Sensorimotor cortex	4	−40	−10	56	6.69				
Superior parietal lobe	40	−50	−38	50	9.92				
		−40	−46	54	9.69	48	−42	44	6.60
		−34	−52	52	9.39	34	−56	52	9.42
	7					12	−58	54	8.79
1-back > 0-back									
DLPFC	46	42	36	18	7.49				
	46	20	20	7.34					
	9	42	30	38	6.97				
Superior frontal gyrus	6	−36	4	24	6.71	38	14	48	6.68
2-back > 0-back									
Anterior cingulate	32					4	24	42	9.25
DLPFC	46					36	36	16	8.50
	9					40	30	35	6.26
Inferior frontal gyrus	44	−42	14	24	6.85	50	10	18	7.12
Superior frontal gyrus	6	−40	4	38	6.56	40	10	44	6.67
Superior parietal lobe	40	−44	−50	44	7.72	42	−58	48	7.42
	7	14	−62	52	7.13	−14	−68	50	6.35
b: Decreases									
Rest > 0-back									
Posterior cingulate	31					12	−44	38	8.65
						10	−30	34	8.23
Rest > 1-back									
Medial frontal gyrus	9	0	56	32	6.71				
Posterior cingulate	30	−10	−52	8	10.19				
	30	−28	−44	2	6.44				
	23/31	−5	−56	15	9.83				
	31	−2	−34	38	7.84				
Superior temporal gyrus	42					40	−14	8	6.26
Inferior occipital gyrus	18					32	−88	−4	7.17
Rest > 2-back									
Medial frontal gyrus	10	0	54	18	6.97	14	56	−2	6.75
		−12	62	12	8.99	8	55	14	7.04
Posterior cingulate	23/30	−6	−58	12	11.56				
	30	−2	−52	22	10.89				
	31					8	−42	32	10.58
0-back > 1-back	None								
0-back > 2-back	None								

BA = Brodmann Area; DLPFC = Dorsolateral Prefrontal Cortex.

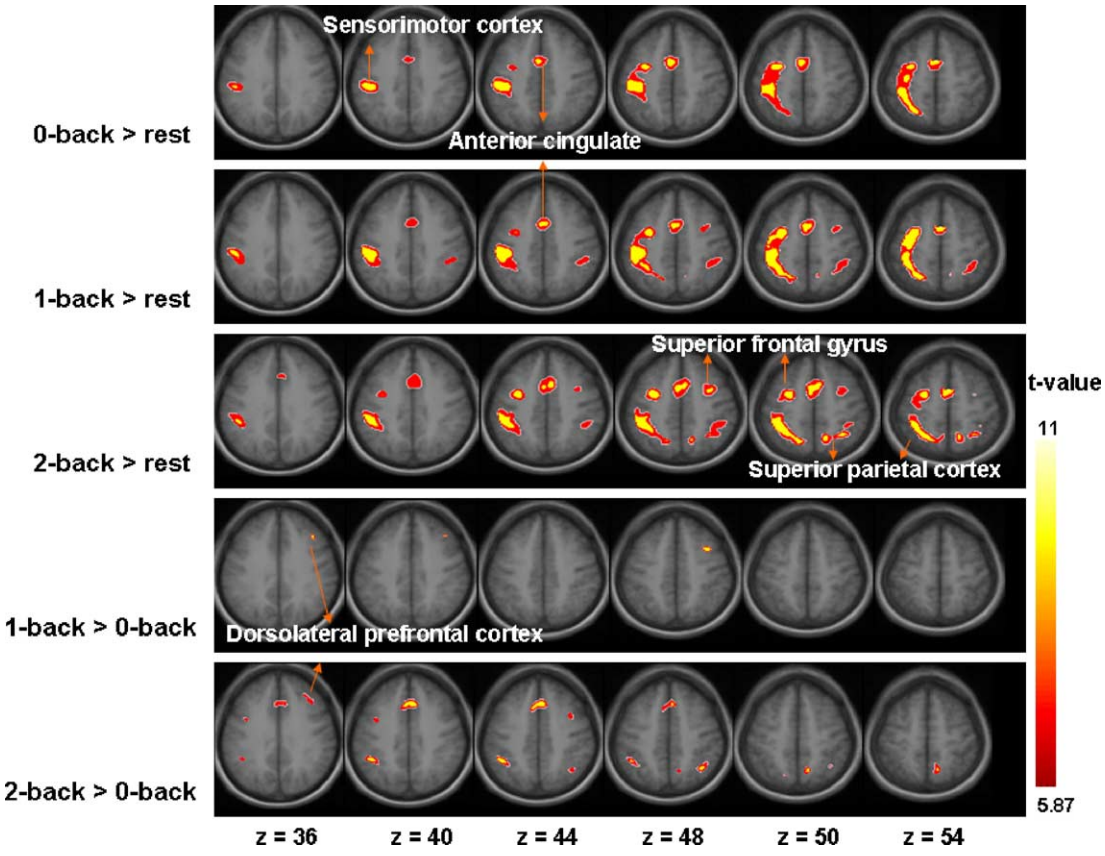

Fig. 3. Generic, group activation maps. One-sample *t* tests of activity, collapsed across rivastigmine and placebo groups, are shown for 0-, 1- and 2-back versus rest and 1- and 2-back versus 0-back comparisons (threshold $P = 0.05$; voxel-level correct). These effects are reported in order to facilitate comparison of our study sample with that of previous fMRI studies of schizophrenia patients using an '*n*-back' task (see Discussion). Left hemisphere is shown on the left of the axial view.

memory load, were in the expected direction and in line with previous findings of combined attention and working memory effects under cholinergic enhancement (Bentley et al., 2004), the magnitude of this effect was rather small suggesting that cholinergic facilitation with this drug (at doses known to be effective for cognitive symptoms in AD) in schizophrenia patients treated with atypical antipsychotics may not produce clinically meaningful cognitive improvement (assuming that cognitive improvements with medium-to-large effect sizes would be clinically meaningful). It seems reasonable to suggest that double-blind studies so far have failed to provide convincing data for the hypothesis that AChE-Is may lead to meaningful cognitive improvement when added to atypical antipsychotics in schizophrenia patients. One explanation for the limited range of this augmentation strategy is that the pathophysiology of cognitive impairment in schizophrenia patients is different to that seen in AD patients (also see The influence of smoking and concurrent medication). Interestingly, even in AD patients, procholinergic treatments are generally more effective in preventing further cognitive decline rather than producing a marked improvement and there is some recent evidence that this effect may be more marked in those receiving hypertensive drugs (Rozzini et al., 2005).

There was some decrease in symptom scores in the rivastigmine group, but this also did not emerge as a significant interaction because of a decrease, though of much less magnitude, also in the placebo group (Table 2). This placebo response may reflect the increased clinical care offered to all patients of this study. The absence of noticeable gastrointestinal side effects in rivastigmine treated patients in this study was perhaps related to the use of antipsychotics which act as antiemetics because of their dopamine blocking actions (Arnt and Skarsfeldt, 1998).

Rivastigmine and neural activity

Unlike the neural effects of rivastigmine in patients with AD (see Introduction) and of galantamine in patients with mild cognitive impairment (Goekoop et al., 2004), we did not find an increase in fMRI activity within the frontal working memory areas. It may relate to the fact that we had examined patients treated with atypical antipsychotics which might have already restored frontal activity (Honey et al., 1999; Braus et al., 2001, 2002; Mendrek et al., 2004). In the present study, a network comprising frontal and parietal regions was activated at baseline, with no differences between the patients who later received placebo or rivastigmine. These observations are, in general, congruent with previous studies of working memory in normal subjects and patients which have reported involvement of the frontal and parietal regions (review, Smith and Jonides, 1997; Callicott et al., 1999; Honey et al., 1999). Decreased task-related frontal activity as part of schizophrenia is well recognized, with reduced DPLFC activation during '*n*-back' tasks and a normalization of fMRI signals in this region with atypical antipsychotic

treatment (Honey et al., 1999). Given that we detected significant DLPFC and anterior cingulate activation with the 2-back condition even at baseline (Table 4, Fig. 3) and that our patients were on atypical antipsychotics, it is probable that at least a partial restoration of brain response in frontal regions (Honey et al., 1999; Braus et al., 2001, 2002; Mendrek et al., 2004) had already occurred. Atypical antipsychotics are found to improve cognitive functions with putative frontal lobe involvement such as verbal working memory (Green et al., 1997), verbal fluency (Lee et al., 1994) and executive functioning (Rossi et al., 1997) with medium-to-large effect sizes (review, Woodward et al., 1997). It is perhaps not surprising that we failed to observe enhancement of frontal activity with rivastigmine in our sample given the small and non-significant change in working memory accuracy (and no change in RT) with this treatment. The lack of significant improvement in performance, however, was not due to the ceiling effect (see Fig. 1, 2-back condition): The baseline performance of our patients at the 2-back condition was well below the ceiling (i.e. 1005) and lower than performance of healthy individuals seen in other studies at the 2-back condition of '*n*-back' tasks with similar cognitive demands [mean (SD) accuracy = 84.76% (±19.56) in Kumari et al., 2003b; 83% (±14.3%) in Glabus et al., 2003].

In healthy subjects, indirect cholinergic enhancement through administration of the AChE-I physostigmine at a fixed low working memory load or during visual attention has been associated with enhanced activity outside the working memory network in extrastriate cortex (Furey et al., 2000; Bentley et al., 2004) and, for working memory tasks, with a decrease (failure to increase compared to the control state) in activity in frontal working memory areas (Furey et al., 1997, 2000). We found that rivastigmine increased activation outside the network in the middle occipital gyrus at 12 weeks over baseline, compared to that found under placebo, across differing working memory loads. This region receives cholinergic innervations (Selden et al., 1998) and is known to have an important role in visuospatial attention (Mangun et al., 1998; Martinez et al., 1999; Beauchamp et al., 2001) likely to be helpful to the theorized slave system of visuospatial sketchpad in working memory (Baddeley, 1986). In previous cholinergic augmentation studies, it has been proposed that the increase in this region relates to enhanced perceptual processing during working memory encoding and enhanced visual attention (Furey et al., 2000; Bentley et al., 2004). We also found an increase in brain activity for the 0-back > rest contrast within the right superior frontal gyrus at 12 weeks over baseline under placebo but not rivastigmine. Although the functional significance of this finding (in placebo) is uncertain, a similar influence of cholinergic enhancement in the same regions has been described in previous studies of healthy subjects. Specifically, Furey et al. (1997) found that under placebo, activity in right superior lateral frontal cortex increased during a working memory task compared to rest, an increase that was absent during cholinergic augmentation with physostigmine.

The influence of smoking and concurrent medication

In order to study a representative sample of the patient population, we included smokers (most schizophrenia patients smoke; Hughes et al., 1986) and a variety of atypical antipsychotic treatments in our study group. Anticholinergic medication was an exclusion criterion (see Materials and methods) as this would interact with the cholinergic augmentation and is known to impair cognitive and information processing functions in both normal (Kumari et al., 2001; Zachariah et al., 2002) and schizophrenic populations (Strauss et al., 1990; Ettinger et al., 2003; Kumari et al., 2003a,b). Eight of the 11 patients who received rivastigmine treatment were regular cigarette smokers. Cigarette smoking is considered to desensitize nicotine receptors in patients with schizophrenia who do not show the normal upregulation following chronic nicotine use (review, Kumari and Postma, 2005). This might have prevented the ChE-I reaching full therapeutic potential, influencing changes in brain activity as well as improvements in behavioral performance or clinical status. Future studies might wish to examine the cognitive effects of ChE-Is in non-smoking schizophrenia patients and to use allosterically potentiating ligands (Friedman, 2004), such as galantamine (Maelicke et al., 2001), which inhibit cholinesterase and, at the same time, enhance nicotinic receptor sensitivity in the presence of ACh by binding to the nicotinic receptor (Schrattenholz et al., 1996) to improve cognitive functions in smoking schizophrenia patients. In addition to the possible effect of smoking, the differences in concurrent antipsychotic medication may also have some effects on our results. Of the five patients in the rivastigmine group showing the most increases (averaged across all loads) in the middle occipital gyrus, two were on olanzapine, two on quetiapine and one on risperidone, so this effect of rivastigmine does not seem to be specific to the use of any particular atypical antipsychotic. It is, however, possible that procholinergic stimulation has weaker effects in patients treated with olanzapine than in those with risperidone and quetiapine since six of 11 patients assigned to receive rivastigmine were on olanzapine (with only two on risperidone and three on quetiapine) and, of these six, only two showed this change. Olanzapine has some anticholinergic actions (Arnt and Skarsfeldt, 1998) which may counteract potential procholinergic effects of rivastigmine.

Conclusion

This investigation revealed significant increases in brain activity in the middle occipital gyrus but not in any areas within the working memory neural network and no significant changes in behavioral and clinical measures with rivastigmine treatment (compared to placebo), at doses known to be effective for cognitive symptoms in AD. The areas influenced by the drug are consistent with those identified in previous studies of healthy subjects with cholinergic augmentation in association with enhanced perceptual processing during working memory encoding and enhanced visual attention. Future studies need to establish the cognitive and neural effects of procholinergic and/or allosterically potentiating ligands in non-smoking as well as smoking schizophrenia samples.

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