Psychopharmacology (2006) 185: 339–347
DOI 10.1007/s00213-006-0334-2

ORIGINAL INVESTIGATION

Emma J. Rose · Enrico Simonotto · Edgar P. Spencer · Klaus P. Ebmeier

The effects of escitalopram on working memory and brain activity in healthy adults during performance of the *n*-back task

Received: 26 September 2005 / Accepted: 19 January 2006 / Published online: 9 March 2006

Abstract *Rationale:* Psychotropic medication affects cognition and brain function, making it a potential confounder in functional neuroimaging studies of psychiatric patients. *Objective:* To determine whether the sub-acute administration of an antidepressant (escitalopram) would induce differences in cognitive performance and associated brain function, which could be observed within the normal power of a functional imaging study. *Materials and methods:* Healthy adults (N=10) received a short course of escitalopram (10 mg/day for 7 days). Participants performed a parametric working memory (WM) task during BOLD fMRI, both while medication-free and after medication. To control for order effects, the medication-free examination was completed by half the subjects before starting medication and by the other half at least one week after medication. *Results:* Escitalopram had no significant effect on WM accuracy or reaction time. Preliminary analysis of the imaging data revealed no significant ($p_{corrected}<0.05$) differences in memory-load-dependent activation between conditions. However, small volume correction analysis of regions that were significant prior to correction for multiple comparisons highlighted between condition differences in regions likely to be susceptible to antidepressant effects (i.e. thalamus, anterior cingulate and inferior frontal gyrus). *Conclusions:* These results suggest that the sub-acute administration of antidepressants in healthy controls does not affect cognitive or hemodynamic function in healthy adults to a magnitude greater than one standard deviation unit. Therefore, the confounding effect of antidepressants on signal intensity in imaging studies of medicated, depressed individuals may be limited.

Keywords Escitalopram · Working memory · Major depression · Functional MRI

E. J. Rose · E. Simonotto · K. P. Ebmeier (✉)
Department of Psychiatry, University of Edinburgh,
Kennedy Tower, Morningside Park,
Edinburgh, EH10 5HF, UK
e-mail: k.ebmeier@ed.ac.uk
Tel.: +44-131-5376505
Fax: +44-131-5376505

E. J. Rose · E. Simonotto · K. P. Ebmeier
SHEFC Brain Imaging Research Centre for Scotland,
Department of Clinical Neurosciences,
Western General Hospital,
Crewe Road,
Edinburgh, EH4 2XU, UK

E. J. Rose
Intramural Research Programme,
National Institute on Drug Abuse,
Baltimore, MD, USA

E. P. Spencer
Medical Toxicology Unit, Guys' and Saint Thomas' Hospital,
London, UK

Introduction

The absence of cognitive side effects of antidepressant medication enhances patients' treatment compliance (Amado-Boccara et al. 1995). A disruption of cognitive function resulting from antidepressant medication, however, is not only of clinical concern; it is also an important confounder in empirical investigations of major depressive disorder (MDD). It is important, therefore, in studies of cognition and brain function to identify and quantify changes that are associated with antidepressants.

In contrast to tricyclic antidepressants (TCAs), the selective serotonin reuptake inhibitors (SSRIs) appear to have little or no detrimental effect on simple or complex psychomotor performance (e.g. Fairweather et al. 1996, 1997; Hindmarch 1988). Indeed, there is evidence to suggest that SSRIs may actually facilitate psychomotor function (e.g. Hindmarch and Bhatti 1988; Hindmarch and Harrison 1988; Hasbroucq et al. 1997; Loubinoux et al. 2005; Nathan et al. 2000a,b) and other aspects of cognitive function, such as information-processing capacity (Nathan et al. 2000a,b). An early review of the effects of long-term drug administration in normal, healthy volunteers failed to find evidence of a significant effect on either short-term memory (STM) or long-term memory (LTM) after either TCA or SSRI treatment (Amado-Boccara et al. 1995).

However, more recent studies suggest that, while having no effect on immediate recall, the acute administration of some SSRIs enhances delayed recall and recognition in LTM (Harmer et al. 2002). Moreover, there may be a differential effect of SSRIs, depending on the affective nature of stimuli that are used in tests of memory and perception. For example, sub-acute administration of citalopram or reboxetine to healthy controls (i.e. 20 or 8 mg/day, respectively, for 7 days) has been shown to reduce the identification of negative faces and enhance recall of positive emotional material in the absence of any significant alteration of the affective state of participants (Harmer et al. 2004). Thus, there is some controversy in the literature as to whether SSRIs facilitate cognitive function in a general or specific manner or whether they have no significant effect.

Relatively few neuroimaging studies have considered the direct effects of antidepressants on brain function. There are, however, a handful of studies that have noted significant effects in both normal, healthy and MDD samples. In healthy participants, SSRIs alter blood flow in thalamus, hypothalamus and cingulate cortex (Geday et al. 2005) and result in changes in brain activity (e.g. Del Ben et al. 2005; Mckie et al. 2005). For example, a single administration of i.v. citalopram was shown to result in a time-dependent increase in activation in the hippocampus, caudate, amygdala, striatum and thalamus (Mckie et al. 2005) and a significant attenuation of activation in response to aversive stimuli in a 'Go–NoGo' task in both Brodmann Area (BA) 47 and the right amygdala (Del Ben et al. 2005). An attenuation of activation was also seen in BA 11 in response to reward (vs loss) conditions. Similarly, alterations in brain metabolism are associated with clinical response in patients with MDD on antidepressants (e.g. Davidson et al. 2003; Davies et al. 2003; Drevets et al. 2002; Kalin et al. 1997; Kennedy et al. 2001; Mayberg et al. 2000). Such alterations are commonly seen in areas that are functionally altered in MDD, such as the frontal and limbic cortices (e.g. Kennedy et al. 2001; Mayberg et al. 2000), and, in particular, the anterior cingulate cortex (ACC; Davidson et al. 2003; Drevets et al. 2002; Kennedy et al. 2001; Mayberg et al. 2000). A significant association between rCBF pretreatment and treatment outcome in some studies supports the relationship between blood flow and treatment response (e.g. Saxena et al. 2003).

The investigation of brain-behaviour responses to antidepressants is confounded by a variety of factors. For example, an improvement of the affective state associated with antidepressant treatment may account for the functional changes noted in post-treatment studies of depressed patients. There may be an interaction between medication and affective state. Antidepressants may directly or indirectly affect the nature of the observed signal in specific neuroimaging methods, e.g. antidepressant-induced changes in blood volume or flow could result in global or regional changes in the observed BOLD signal. In light of data that are indicative of notable metabolic antidepressant effects in both normal, healthy individuals and clinical populations, it is important to quantify the contribution of such effects in functional neuroimaging studies of MDD.

The aim of this investigation was to determine whether a short course of an SSRIs (escitalopram) given at a typical clinical dose would affect brain function measured using BOLD EPI fMRI during the performance of a working memory task (the *n*-back task) in normal, healthy volunteers. In light of previous evidence of a facilitatory effect of SSRIs on both psychomotor function and LTM, it was hypothesized that escitalopram would facilitate WM performance and would lead to alterations in brain metabolism in regions commonly associated with the affective profile of treatment-responsive MDD patients.

Materials and methods

The study was approved by the Lothian NHS Board, Psychiatry and Psychology Research Ethics Committee and the management board of the Lothian Primary Care NHS Trust. Written informed consent was obtained from all participants.

Design

A counter-balanced crossover cohort design with within-subjects factors of medication status (medication-free vs post-medication) and level of difficulty of the *n*-back task (0-, 1-, 2-, and 3-back) was employed. Analysis focused on the effect of these factors upon accuracy (percentage correct) and reaction time (RT/ms) on the *n*-back task.

Participants

Participants (N=10, right-handed, seven male; mean age=24.6 years, mean estimated IQ=106.0, mean years of education=15.1) were opportunistically sampled from the general population. Exclusion criteria included any history of significant or relevant physical illness (including, but not limited to, heart attack, stroke, diabetes, liver disease, or other major physical illness), psychiatric or neurological illness; pregnancy; implanted metallic objects; and the consumption of any psychoactive or vasoactive medications. Participant eligibility was confirmed by their general practitioner (GP). Two participants identified themselves as suffering from mild dyslexia after consent. Given that we were interested in a visuospatial, as opposed to verbal, variant of the *n*-back task and in brain regions outside of the network of areas that show abnormal activity in dyslexic adults and children (see Shaywitz and Shaywitz 2005 for a review), both of these participants were retained in the study. Volunteers received £50 for expenses.

Materials and procedure

Affective assessments Prior to each scanning session, participants completed the Beck Depression Inventory (BDI; Beck et al. 1961), the Stress Arousal Checklist (SAC; Mackay et al. 1978), and the Alderley Park State Anxiety Questionnaire (APSAQ; Walker 1990). These self-assessment measures provide estimates of the presence/absence of depression, state stress and arousal and state anxiety, respectively.

Neuropsychological assessments For eight participants, the National Adult Reading Test (NART; Nelson and Willison 1991) was used to estimate full-scale Wechsler Adult Intelligence Scale- Revised (WAIS-R; Wechsler 1981) IQ. However, given that dyslexia is a disorder that may confound performance on the NART, the two participants who identified themselves as dyslexic instead completed a short-form of the WAIS-R, which consisted of four non-verbal WAIS-R subtests ('information', 'picture completion', 'arithmetic' and 'block design), and has been shown to provide reliable estimates of full-scale WAIS-R IQ (Guilmette et al. 1999).

In addition to WM, participants also completed other cognitive measures. Two subtests of the Test of Everyday Attention (TEA; Robertson et al. 1994), i.e. the Elevator Counting with Distraction (ECD) and Visual Elevator (VE) tasks were used to measure auditory selective attention and cognitive flexibility, respectively. These tasks are sensitive to aspects of cognitive function that have been noted as being impaired in MDD, and are assumed to be reliant on the integrity of frontal lobe function, which has been shown to alter by SSRI medications in both normal, healthy and MDD participants. Participants also attempted the Rey Auditory Verbal Learning Test (RAVLT; Rey 1964), which assesses learning and memory (constructs that may also be affected by SSRIs). In the RAVLT, participants learn a list of 15 words (List A), over five learning trials. They are then given a single trial on which to learn a new list (List B), after which there is an immediate and then a delayed test of retention of items from the initial list. These additional cognitive measures were completed prior to each scanning session.

A block-design paradigm was employed during functional imaging. During fMRI, participants undertook a visuospatial version of the *n*-back task. Variations of the *n*-back task have been used in both clinical and non-clinical populations (e.g. Callicott et al. 1999; Casey et al. 1998; Gevins and Cutillo 1993; Jansma et al. 2000; Nystrom et al. 2000). The variant of the *n*-back task used in this study involved the presentation of blocks of images of four numbered boxes. A coloured dot appeared in one of the boxes, the position of which was varied between images. Participants pressed the button corresponding to either: (a) the dot's current position (0-back); (b) its position in the previous picture (1-back); (c) its position two pictures previously (2-back); or (d) its position three pictures previously (3-back). There were 14 images in each 1-, 2- or 3-back block while each 0-back block had nine images. The inter-stimulus interval was 3 s, and the task level to be attempted for a given block was indicated by a 3-s prompt screen. Participants completed a full practice run of the *n*-back task (10 blocks each of the 1-, 2-, and 3-back levels, each separated by a block of 0-back) after screening and prior to scanning. Within each scanning session, participants also completed ten sets of each of the *n*-back trials, spread over two acquisition phases, consisting of five blocks each of 1-, 2-, and 3-back trials.

Medication Participants received 10 mg/day of escitalopram ('Cipralex'/'Lexapro') for 7 days. Escitalopram is the pure *S*-enantiomer of the racemic bicyclic phthalane derivative citalopram. In comparison to its parent compound, it can be administered in lower effective doses and with reduced side effects.

Functional MRI BOLD echo planar imaging (EPI) with TR=2.5 s, TE=40 ms, 90° flip angle, 24 cm field of view, and a 64×64 in-plane resolution was carried out in a 1.5-Tesla GE Signa MRI scanner fitted with echo speed gradients and using the standard head coil. Functional images were acquired in the para-axial plane, with a slice thickness of 5 mm. Data were acquired in two functional imaging sessions, with each functional acquisition period lasting 18 min and 55 s. Structural images (T1- and T2-weighted) were also acquired for each participant.

Integrated Functional Imaging System (IFIS; PST: Pittsburgh, PA, USA) software and hardware were used to present the WM paradigm and to log behavioural responses. Task instructions and stimulus items were presented on an LCD display mounted on the head coil. Participants responded to each item using ergonomically shaped pushbutton units, which had a button located underneath the thumb and each fingertip. Participants were instructed as to which pushbutton corresponded to each response type (i.e. thumb=1, index finger=2, etc.).

Imaging analysis Functional imaging data were analysed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). BOLD EPI images were reconstructed to ANALYSE format (Mayo Foundation, Rochester, MN, USA). These images were registered to their mean; the mean co-registered to the T1-image, the T1-image spatially normalized and the transformation to normalize the T1-image was then applied to the co-registered EPI images. A linear affine transformation was used, followed by non-linear deformation; images were re-sampled using sinc interpolation to cubic voxels of size 8 mm^3. Normalized images were then smoothed spatially to minimize residual inter-participant differences, using a 3-D Gaussian filter (6×6×6 mm^3 FWHM). Initially, fixed-effects contrasts were constructed for each participant that determined regions of significantly altered activity associated with the linear increase in difficulty of the *n*-back task. Second-level random-effects contrasts were then constructed for the group both within- and between-conditions. Coordinates of significant clusters ($p_{corrected}<0.05$) were con-

verted from MNI to Talairach space (Talairach and Tournoux 1988), using a non-linear transformation. The anatomical location of significant clusters was determined using the Talairach Daemon Database (Lancaster et al. 1997, 2000). Whole brain [rather than region of interest (ROI) analysis] was used to determine the global effect of escitalopram on brain activity, rather than just in regions presumed to be involved in working memory or those regions associated with MDD. However, to partially address the reduced power of the whole brain analysis, a secondary, small volume correction (SVC) analysis (i.e. 5-mm sphere, with fixation point at the local maxima) was conducted for those clusters with a previously demonstrated effect of antidepressant medication, and which were significant ($p_{\text{uncorrected}}<0.001$) in the between-condition comparison.

Procedure Participants were allocated to one of two subgroups. Group A completed their first test session, which included all affective, cognitive and neuroimaging assessments, on the same day as screening (i.e. Day 1). They then took 10 mg/day of escitalopram for the after 7 days. On the final day on which they took escitalopram (i.e. on Day 8), and not more than 6 h after they had taken the final dose, they completed the second test session. Session 2 mimicked session 1, but did not include *n*-back training or IQ assessment. Group B completed the same assessments, although the order of medication-free and post-medication scans for this group was reversed, such that after pre-scanning assessment (i.e. on Day 1) group B participants were given their medication, which they took for 7 days before returning to their first scanning session (i.e. on Day 8). Individuals in this group then remained medication-free for 7 days prior to returning for their second scanning session (i.e. on Day 15).

On the day of their post-medication scan, participants provided a blood sample (10 ml collected from an antecubital vein into lithium heparin tubes) prior to scanning. Plasma was separated by centrifugation and stored in clearly labelled tubes at −20°C. Blood plasma was analysed for total *S*-citalopram and total *N*-desmethylcitalopram (norcitalopram) using high-performance liquid chromatography.

Results

Medication The average time between the final dose of escitalopram and scanning was 230 min (s.d.=78.59, minimum=115, maximum=340). High-performance liquid chromatography analysis of blood plasma detected *S*-citalopram (range=0.01–0.03 mg/l) in all participants, and *N*-desmethylcitalopram (minimum=0.01 mg/l) in six individuals.

Affective assessments (See Table 1): Paired-samples *t*-tests revealed that there was no significant difference in the mean BDI and SAC scores of participants pre- and post-medication. However, sub-acute administration of escitalopram did result in a significant increase in the magnitude of self-rated state anxiety ($t_{(9)}=2.17$, $p=0.03$), as measured using the APSAQ. Included in this assessment are statements pertaining to both affective and physical symptoms of anxiety (e.g. 'I feel I can cope', 'I have butterflies in my stomach'). Participants received a single score on this measure, summarizing changes in cognitions, emotions or physical symptoms related to anxiety, thus, making it difficult to ascertain whether changes in score between conditions were the result of subjective feelings of anxiety or alterations in more objective symptoms (e.g. physical restlessness).

Behavioural assessments Participants received two accuracy scores (an absolute score and a scaled score) for each TEA subtest. On the VE task, participants also received absolute and scaled RT scores, based on the average time (in seconds) taken to make attentional switches on those items that they correctly responded to. Scaled scores for the TEA subtests take into account the absolute score and the age-dependent normal distribution of scores. Paired-samples *t*-tests revealed no statistically significant differences before and after medication on either of the TEA measures, suggesting that the sub-acute administration of escitalopram did not significantly affect auditory selective attention, cognitive flexibility or psychomotor function.

Several outcome measures can be derived from the RAVLT: novel learning, interference of novel learning with prior learning and the type and number of errors made. A 5×2 (learning trial×medication status) within-subjects ANOVA, examining novel learning, revealed a main effect of learning trial $F_{(4,\ 36)}=33.00$, $p<0.001$), but no main effect of medication status and no interaction between these factors were seen. Post-hoc paired Bonferroni-corrected *t*-tests indicated a significant ($p_{(\text{corrected})}\leq 0.0125$) difference in the mean number of items recalled between the first and second and between the second and third trials ($t_{(9)}=-4.64$, $p=0.001$ and $t_{(9)}=-4.20$, $p=0.002$, respectively). The effect of the interfer-

Table 1 Average score and distribution of scores on each of the affective measures: medication-free versus post-medication

	Medication-free		Post-medication		Paired difference mean (SD)
	Mean (SD)	Min–max	Mean (SD)	Min–max	
BDI	2.0 (2.9)	0–9	3.6 (3.3)	0–10	−1.6 (3.2)
SAC—Stress	7.7 (1.1)	5–9	7.3 (1.5)	5–9	+0.4 (1.2)
SAC—Arousal	6.0 (2.2)	1–9	6.3 (1.9)	3–10	−0.3 (2.7)
APSAQ	16.5 (3.0)	12–22	19.3 (3.2)	13–24	−2.8 (4.1)

ence learning trial on the subsequent recognition of previously learned items was also examined. A paired *t*-test comparison of the extent of interference (i.e. the difference in the number of words from the original list recalled before and after interference learning) experienced before and after medication revealed no statistically significant effect of sub-acute administration of escitalopram on the interference effect.

The n-back task Accuracy and RT data obtained during performance of the *n*-back task were each analysed using a 2×2×4 (medication status×within-scan session×task difficulty) within-subjects ANOVA (see Fig. 1). There was a significant main effect of task difficulty for both accuracy and RT ($F_{(1.48,\ 13.27)}$=8.26, p=0.008 and $F_{(1.73,\ 15.54)}$=48.67, p<0.001), a significant main effect of scanning session ($F_{(1,\ 9)}$=9.47, p=0.013) on RT and a significant interaction between session and difficulty ($F_{(3,\ 27)}$=6.83, p=0.001) on RT also. However, there was no significant main effect of medication status on the accuracy or RT, and no other interactions reached significance. Linear contrasts for the effect of *n*-back on accuracy and RT ($F_{(1,\ 9)}$=12.32, p=0.007 and $F_{(1,\ 9)}$=9.47, p=0.013) and for the level of *n*-back and the interaction between session and difficulty ($F_{(1,\ 9)=}$16.29, p=0.003) were also significant. Post-hoc paired-samples *t* tests, again using Bonferroni correction, demonstrated that participants were significantly faster to respond to 0-back items in the second functional imaging acquisition session ($t_{(9)}$=4.74, p=0.001); however, all other comparisons of RT between sessions were non-significant.

fMRI Results (see Fig. 2)

Medication-free condition Memory-load-dependent increases in activity were noted in the left hemisphere (LH) in a cluster comprising both superior and inferior parietal lobes, and in the precentral gyrus, bilaterally in the middle and superior frontal gyri, and in the right hemisphere (RH) in the cerebellum. Load-dependent decreases occurred in the left middle, inferior and superior frontal, angular and middle temporal gyri and in a LH cluster of activation comprising the claustrum and the superior temporal gyrus. Significant decreases were also seen in the RH in the pre- and post-central gyri, in the cerebellum, and in the parahippocampal and superior temporal gyri, and in a number of inter-hemispheric clusters with local maxima in the lingual, middle occipital and medial frontal gyri.

Post-medication condition Memory-load-dependent increases were found in the LH in the insula and in a cluster involving the inferior and superior parietal lobules and the precuneus. Significant increases were also seen in the RH in the insula and inferior and middle frontal gyri, and in two interhemispheric clusters—both encompassing the superior and middle frontal gyri (one more anterior than the other, i.e. BA10 and BA6). Significant decreases in activity were noted in the LH in the middle temporal and angular gyri, the lingual gyrus and the hippocampus, in the RH in cingulate gyrus and in interhemispheric clusters, i.e. in the superior frontal gyrus, the cuneus, and the cingulate gyrus.

Medication-free vs post-medication Random effects, paired-samples *t*-tests revealed no clusters of statistically different (increase or decrease; $p_{\text{corrected}}$<0.05) activation between medication-free and post-medication conditions. Thus, suggesting that the sub-acute administration of escitalopram did not have a differential effect on either regional or global brain activity during the performance of the *n*-back task. However, as noted, the whole-brain analysis used to compare conditions and the correction for multiple comparisons may have been too conservative given the within-subjects nature of this study and the small sample size. Therefore, a secondary ROI analysis was

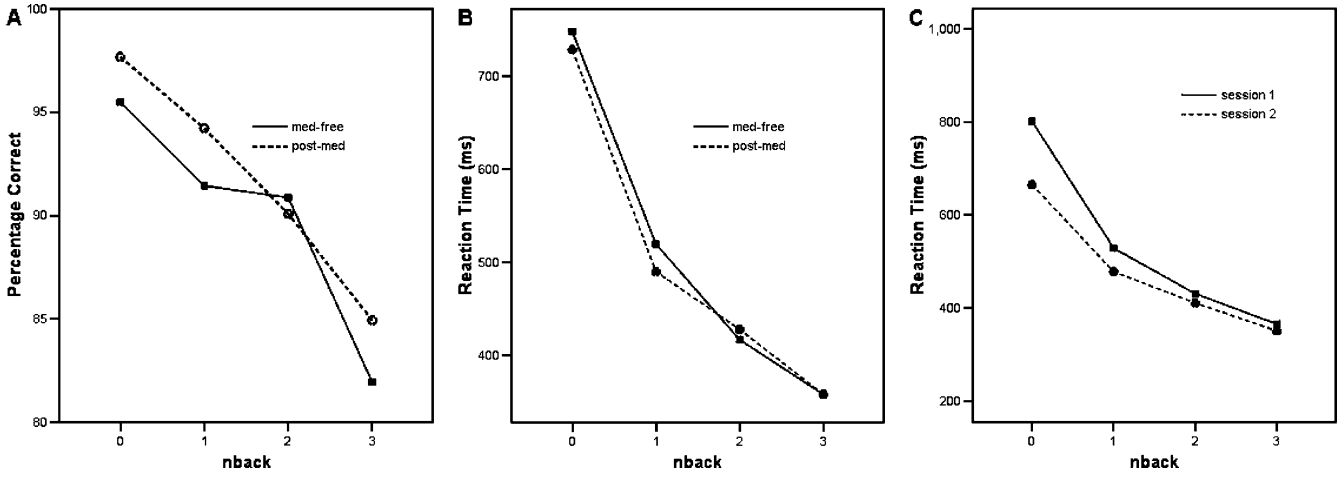

Fig. 1 **a** Mean accuracy (percentage correct) of participants at each level of *n*-back before and after taking a sub-acute dose of escitalopram (i.e. 10 mg/day for 7 days); **b** mean reaction time of participants (ms) at each level of *n*-back before and after the sub-acute administration of escitalopram; **c** mean reaction time at each level of *n*-back during the first and second functional imaging acquisition sessions, irrespective of medication status

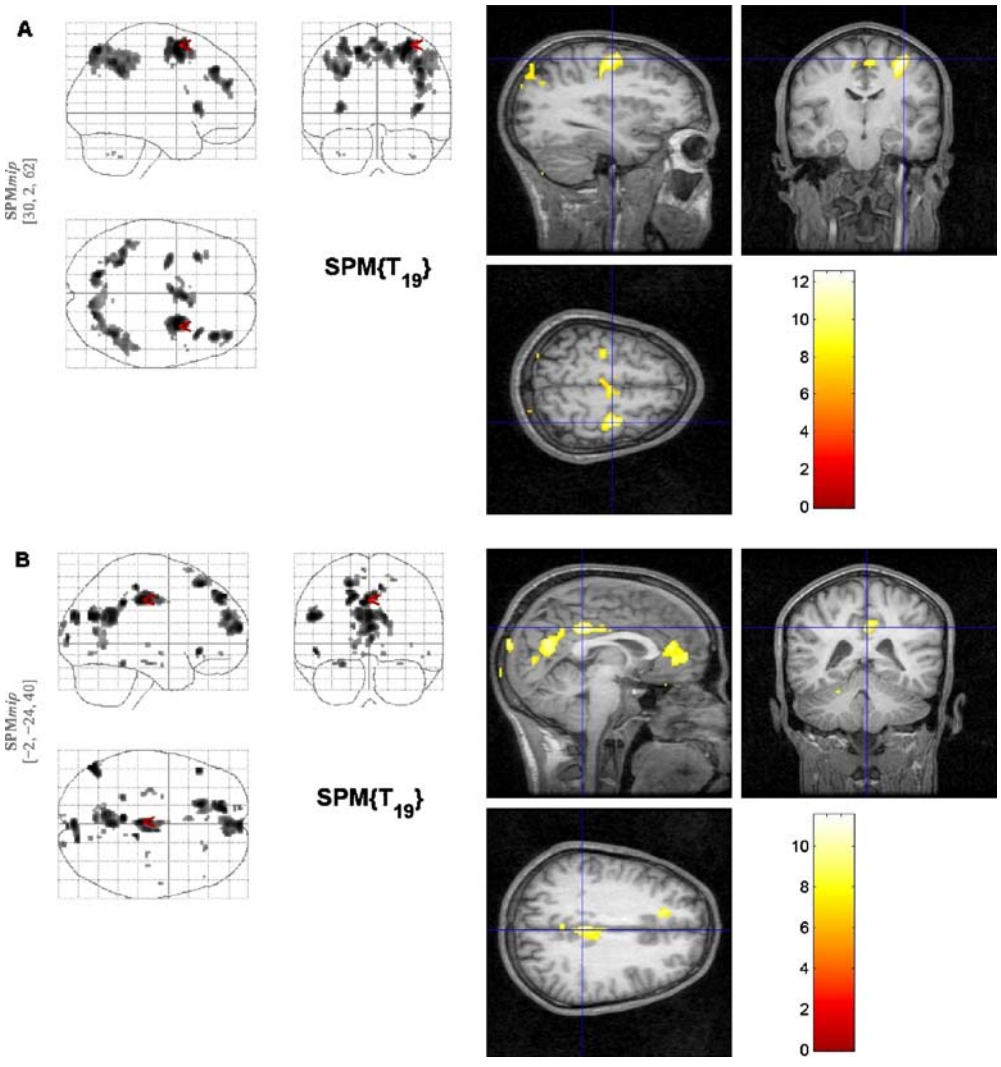

Fig. 2 Regions of significant activation for participants across all scanning sessions (i.e. both medication-free and post-medication scans): **a** clusters of statistically significant increase associated with the linear increase in difficulty of *n*-back (i.e. random effects, $p_{corrected}<0.05$); **b** clusters of statistically significant decrease associated with the linear increase in difficulty of *n*-back (i.e. random effects, $p_{corrected}<0.05$). Both image pairs highlight the global maxima for the given contrast—rendered on glass brain image (from SPM99) and on the T1 structural image for one of the participants in this study

conducted, in which an SVC analysis was conducted on regions that: (1) showed significant load-dependent activation prior to correction and (2) had local maxima in regions that have demonstrated antidepressant-dependent effects in other studies. The results of this analysis (see Table 2) were indicative of load-dependent increases in clusters in the left thalamus, right caudate and right ACC, and load-dependent decrease in the left inferior frontal gyrus. These clusters were small (range=8–32 mm^3), and one, therefore, has to be cautious in interpreting their significance.

Table 2 Small volume correction analysis of medication-free vs post-medication conditions—summary of a priori regions (i.e. those areas that have shown drug-dependent changes in activity in other investigations) of significantly increased/decreased activation associated with linear increase in task difficulty

Condition	Contrast	Cluster coordinates (*x*, *y*, *z*)	Hemisphere*	BA	Location	K_E	*z*-score†	Significance ($p_{(corrected)}$)
Medication-free vs post-medication	Increase	−8, −38, 14	LH	25	Thalamus and pulvinar	1	3.30	0.023
		2, 8, −4	RH		Anterior cingulate	3	3.29	0.015
		−22, −28, 6	LH		Thalamus and pulvinar	1	3.21	0.023
		−10, −36, 12	LH		Thalamus and pulvinar	1	3.19	0.023
		16, 24, 8	RH		Caudate and caudate body	1	3.15	0.023
Medication-free vs post-medication	Decrease	−44, 28, −12	LH	47	Inferior frontal gyrus	4	3.38	0.013

Noted in this table are those clusters of significant ($p_{uncorrected}<0.001$) activation which demonstrated significant ($p_{corrected}<0.05$) changes in activity after small volume correction analysis (i.e., 5-mm sphere, with fixation on the local maxima for a given cluster)

Discussion

There was an increase of state anxiety associated with the sub-acute administration of escitalopram, but no increase in stress or arousal, nor any emergence or reduction of symptoms of major depression. Although there are data in healthy adults that suggest an enhancing effect of SSRIs on affective processing in the absence of changes in observed mood, including anxiety (Harmer et al. 2004), animal models of affect have demonstrated that acute administration of SSRIs leads to temporary elevation in anxiety (Burghardt et al. 2004). Similarly, it is not uncommon to observe early elevation of anxiety in patients in the initial phase of SSRI treatment, subsequently followed by a reduction in anxiety (Boyer and Feighner 1992; Goldstein and Goodnick 1998; Gorman et al. 1987; Masand and Gupta 1999). This effect is not seen consistently and is more likely to occur in patients with a tendency to panic. In future investigations, it would be appropriate to include an affective measure to further explore this effect and to determine whether it is associated with post-drug alterations in brain activity.

Sub-acute administration of escitalopram did not have a significant impact upon WM (the *n*-back task), cognitive flexibility (the VE task), auditory selective attention (the ECD task), verbal learning and recall (both immediate and delayed; the RAVLT), or on psychomotor performance (the VE and the *n*-back). This contradicts those studies demonstrating a post-SSRI improvement in cognition in healthy controls (e.g. Hindmarch and Bhatti 1988; Hindmarch and Harrison 1988; Hasbroucq et al. 1997; Loubinoux et al. 2005; Nathan et al. 2000a,b; Harmer et al. 2002), but is supported by the observations of some other investigations (e.g. Fairweather et al. 1997; Hindmarch 1988, 1995; Hindmarch and Kerr 1994; Nathan et al. 2000b). This may be a consequence of using healthy participants, although a number of studies have shown that both acute and chronic administration of antidepressant medication have a similar impact upon cognitive function in control and clinical populations (Amado-Boccara et al. 1995). Alternatively, in light of data suggesting that the SSRI effect on cognitive function may be associated with the emotional valence of stimuli (Harmer et al. 2004) the lack of an effect on cognition in our study may be due to the neutral nature of the stimuli. Our sample size of ten may have limited statistical power and thus increased the chances of type-II errors. For a post-hoc power calculation, we used the effect size from a previous investigation in which we observed significant group difference on the *n*-back task (Rose and Ebmeier 2006). The results of this analysis suggested that, for Cohen's d=1.21, α=0.05, and β=0.8, a minimum sample size of 20 participants would be required to detect significant behavioural differences. Therefore, we may not have had enough power with ten subjects to detect significant behavioural differences with our sample size, which was typical for a functional neuroimaging study.

The observed memory-load-dependent reduction in RT on the *n*-back task, in conjunction with a decrease in accuracy, could be indicative of a speed/accuracy trade-off as the task became more difficult. However, in previous studies of MDD patients and healthy controls, we found effects of *n*-back difficulty on RT only between 0- and 1-back conditions in the laboratory (Rose and Ebmeier 2006), while there was a load-dependent reduction in RT when the task was performed inside the scanner (Rose et al. 2006). If there is a speed/accuracy trade-off during performance of our version of the *n*-back task then it may be specific to an aspect of the scanner environment (e.g. increased anxiety, increased distractibility etc.). Nonetheless, we were interested in differences associated with administration of escitalopram, and it appears that this effect was consistent across conditions, therefore, even if there is a trade-off it appears not to be differentially affected by the sub-acute administration of SSRI medication.

It has been argued that functional imaging data provide a more sensitive measure of pharmacological effects than cognition or behaviour. However, the whole-brain analyses did not reveal changes in brain activity (increase and decrease associated with the *n*-back task) between medication-free and post-medication sessions. Memory-load-dependent changes were seen in putative WM regions in both conditions (e.g. increased frontal and parietal activity and decreases in a diffuse range of areas). Despite some apparent qualitative differences in the activation maps in the medication-free and post-medication conditions, these did not reach statistical significance between the treatment conditions. Acute administration of citalopram, which contains the same primary active ingredient as escitalopram, appears to affect activation in thalamus, hypothalamus, amygdala and cingulate cortex (e.g. Del Ben et al. 2005; Geday et al. 2005; Mckie et al. 2005), suggesting that our analysis, which controlled conventionally for multiple comparisons, may have been too conservative. Therefore, we conducted a secondary analysis using these areas as a priori small search volumes. This analysis revealed significant changes in these selected areas. There was a post-medication (vs medication-free) decrease in activation in the rostral/subgenual cingulate cortex (BA 24), a region that appears to be significantly more active in MDD patients, compared to controls, during performance of the same WM task (Rose et al. 2006). Moreover, the preliminary fixed-effects analysis also revealed a cluster that was less active post-medication, with a local maximum in the same region (BA 24; K_E=280, p=0.008). The random-effects model used in SPM99, designed to take account of between-subjects rather than within-subjects variation, may have been too stringent for the between-conditions effects that we were interested in.

There are a number of potential limitations to consider when interpreting the study outcomes. First, the sub-acute administration of an SSRI to normal, healthy participants with no history of psychiatric illness may not be comparable to chronic administration in MDD patients. In patients, there is complex interaction of factors (e.g. state affect and medication history), which may contribute to both the cognitive and functional effects of SSRIs. Furthermore, there may be significant differences in the effect of sub-acute vs chronic drug administration and the dose used

here, although representative, was relatively low compared with some clinical drug regimens. Second, while the number of participants was typical of many imaging studies, there is evidence of reduced statistical power (in both cognitive and functional analyses), which could have reduced our ability to detect important between-conditions differences. Other ways to improve our study include a full psychiatric interview with participants prior to participation, a single- or double-blind procedure for drug administration, parallel rather than "crossover" design, but there is clearly a trade-off with participant acceptability and cost. Finally, differences between the outcomes of this study and others (e.g. Harmer et al. 2004) may be due to the route of administration (e.g. oral vs i.v.) and drug dose.

In conclusion, our data indicate preserved cognitive function and brain activation after the sub-acute administration of escitalopram in healthy adults within a sample size typically used in imaging studies. These results clearly require replication and extension with both a larger sample of normal, healthy controls and in clinically depressed, medicated patients, which would allow for the clarification of treatment-specific, illness-specific and interaction effects.

Acknowledgements This work was funded in part by a research studentship from the Medical Research Council (EJR), by a SHEFC Research Development Grant (KPE) and funds from the Gordon Small Charitable Trust (KPE). None of the authors declares an interest that may bias the results presented.

References

Amado-Boccara I, Gougoulis N, Littre MFP, Galinowski A, Loo H (1995) Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 19:479–493

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:53–63

Boyer WF, Feighner JP (1992) An Overview of Paroxetine. J Clin Psychiatry 53:3–6

Burghardt NS, Sullivan GM, McEwen BS, Gorman JM, LeDoux JE (2004) The selective serotonin reuptake inhibitor citalopram increases fear after acute treatment but reduces fear with chronic treatment: a comparison with tianeptine. Biol Psychiatry 55:1171–1178

Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, Goldberg TE, Weinberger DR (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 9:20–26

Casey BJ, Cohen JD, O'Craven K, Davidson RJ, Irwin W, Nelson CA, Noll DC, Hu XP, Lowe MJ, Rosen BR, Truwitt CL, Turski P (1998) Reproducibility of fMRI results across four institutions using a spatial working memory task. NeuroImage 8:249–261

Davidson RJ, Irwin W, Anderle MJ, Kalin NH (2003) The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 160:64–75

Davies J, Lloyd KR, Jones IK, Barnes A, Pilowsky LS (2003) Changes in regional cerebral blood flow with venlafaxine in the treatment of major depression. Am J Psychiatry 160:374–376

Del Ben CM, Deakin JFW, Mckie S, Delvai NA, Williams SR, Elliott R, Dolan M, Anderson IM (2005) The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: An fMRI study. Neuropsychopharmacology 30:1724–1734

Drevets WC, Bogers W, Raichle ME (2002) Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol 12:527–544

Fairweather DB, Ashford J, Hindmarch I (1996) Effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers. Pharmacol Biochem Behav 53:265–269

Fairweather DB, DalPozzo C, Kerr JS, Lafferty SV, Hindmarch I (1997) Citalopram compared to dothiepin and placebo: effects on cognitive function and psychomotor performance. Hum Psychopharmacol 12:119–126

Geday J, Hermansen F, Rosenberg R, Smith DF (2005) Serotonin modulation of cerebral blood flow measured with positron emission tomography (PET) in humans. Synapse 55:224–229

Gevins A, Cutillo B (1993) Spatiotemporal dynamics of component processes in human working memory. Electroencephalogr Clin Neurophysiol 87:128–143

Goldstein BJ, Goodnick PJ (1998) Selective serotonin reuptake inhibitors in the treatment of affective disorders-III. Tolerability, safety and pharmacoeconomics. J Psychopharmacol 12: S55–S87

Gorman JM, Liebowitz MR, Fyer AJ, Goetz D, Campeas RB, Fyer MR, Davies SO, Klein DF (1987) An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 7:329–332

Guilmette TJ, Dabrowski J, Kennedy ML, Gnys J (1999) A comparison of nine WAIS-R short forms in individuals with mild to severe traumatic brain injury. Assessment 6:33–41

Harmer CJ, Bhagwager Z, Cowen PJ, Goodwin GM (2002) Acute administration of citalopram facilitates memory consolidation in healthy volunteers. Psychopharmacology 163:106–110

Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004) Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am J Psychiatry 161:1256–1263

Hasbroucq T, Rihet P, Blin O, Possamai CA (1997) Serotonin and human information processing: fluvoxamine can improve reaction time performance. Neurosci Lett 229:204–208

Hindmarch I (1988) A pharmacological profile of fluoxetine and other antidepressants on aspects of skilled performance and car handling ability. Br J Psychiatry 153:99–104

Hindmarch I, Bhatti JZ (1988) Psychopharmacological effects of sertraline in normal, healthy volunteers. Eur J Clin Pharmacol 35:221–223

Hindmarch I (1995) The behavioral toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 9:13–17

Hindmarch I, Harrison C (1988) The effects of paroxetine and other antidepressants in combination with alcohol in psychomotor activity related to car driving. Hum Psychopharmacol 3(1):13–20

Hindmarch I, Kerr JS (1994) Effects of paroxetine on cognitive function in depressed patients, volunteers, and elderly volunteers. Med Sci Res 22:669–670

Jansma JM, Ramsey NF, Coppola R, Kahn RS (2000) Specific versus nonspecific brain activity in a parametric *n*-back task. NeuroImage 12:688–697

Kalin NH, Davidson RJ, Irwin W, Warner G, Orendi JL, Sutton SK, Mock BJ, Sorenson JA, Lowe M, Turski PA (1997) Functional magnetic resonance imaging studies of emotional processing in normal and depressed patients: effects of venlafaxine. J Clin Psychiatry 58:32–39

Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, Vaccarino FJ (2001) Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am J Psychiatry 158:899–905

Lancaster JL, Summerlin JL, Rainey L, Freitas CS, Fox PT (1997) The Talairach Daemon: a database server for the Talairach atlas labels. NeuroImage 5:S633

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas ES, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131

Loubinoux I, Tombari D, Pariente J, Gerdelat-Mas A, Franceries X, Cassol E, Rascol O, Pastor J, Chollet F (2005) Modulation of behavior and cortical motor activity in healthy subjects by a chronic administration of a serotonin enhancer. NeuroImage 27:299–313

Mackay C, Cox T, Burrows B, Lazzerini T (1978) An inventory for the measurement of self reported stress and arousal. Br J Soc Clin Psychol 17:283–284

Masand PS, Gupta S (1999) Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatr 7:69–84

Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA (2000) Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry 48:830–843

Mckie S, Del Ben C, Elliott R, Williams S, Vai N, Anderson I, Deakin J (2005) Neuronal effects of acute citalopram detected by pharmacoMRI. Psychopharmacology 180:680–686

Nathan PJ, Sitaram C, Stough C, Silberstein RB, Sali A (2000a) Serotonin, noradrenaline and cognitive function: a preliminary investigation of the acute pharmacodynamic effects of a serotonin versus a serotonin and noradrenaline reuptake inhibitor. Behav Pharmacol 11:639–642

Nathan PJ, Stough C, Siteram G (2000b) Serotonin and information processing: a pharmacodynamic study on the effects of citalopram on cognitive and psychomotor function. Hum Psychopharmacol 15:306–307

Nelson HE, Willison J (1991) National Adult Reading Test (NART): test manual. NFER-Nelson, Windsor

Nystrom LE, Braver TS, Sabb FW, Delgado MR, Noll DC, Cohen JD (2000) Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. NeuroImage 11:424–446

Rey A (1964) L'examen de clinique en psychologie. Presses Universitaires de France, Paris

Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I (1994) The test of everyday attention: test manual. Thames Valley Test Company, Bury St. Edmunds

Rose EJ, Ebmeier KP (2006) Pattern of impaired working memory during major depression. J Affect Disord (Dec 15, 2005; E-pub ahead of print)

Rose EJ, Simonotto E, Ebmeier KP (2006) Limbic over-activity in depression during preserved performance on the *n*-back task. NeuroImage 29:203–215

Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr (2003) Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. Am J Psychiatry 160:522–532

Shaywitz SE, Shaywitz BA (2005) Dyslexia (specific reading disability). Biol Psychiatry 57:1301–1309

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, New York

Walker LG (1990) The measurement of anxiety. Postgrad Med J 66: S11–S17

Wechsler D (1981) Manual for the Wechsler adult intelligence scale - revised. The Psychological Corporation, San Antonio, TX