

Original Investigation

Neuronal effects of acute citalopram detected by pharmacoMRI

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Abstract

Rationale Serotonin (5-hydroxytryptamine, 5-HT) is implicated in the aetiology and treatment of a variety of psychiatric disorders. A limitation of research has been the necessity to use indirect measures of 5-HT function.

Method We describe a method of analysing pharmacoMRI data using SPM and apply it to the direct i.v. infusion of selective 5-HT reuptake inhibitor, citalopram, in 12 healthy volunteers. Scanning took place on a 1.5-T Philips MRI scanner.

Results Areas implicated in depression and its treatment were observed to have increasing signal with respect to time. These areas included the caudate, the amygdala, the hippocampus, the striatum and the thalamus.

Conclusion Direct pMRI using i.v. citalopram opens new ways of investigating 5-HT mechanism in depression and its treatment.

Keywords Citalopram - fMRI - Brain - SPM

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is implicated in the aetiology and treatment of a variety of psychiatric disorders including depression, anxiety and impulse-control disorders. This is believed to be due, at least in part, to the involvement of 5-HT in fundamental neuropsychological processes particularly related to aversive stimuli and impulsivity (see Deakin [2003](#)).

Attempts to demonstrate abnormal 5-HT function in patients are limited by the necessity to use indirect measures of 5-HT function, e.g. hormonal response to 5-HT drug challenge or cerebrospinal fluid metabolite concentrations. Advances in brain imaging techniques such as functional imaging (fMRI), structural imaging (VBM) and magnetic resonance spectroscopy (MRS) mean that more direct investigation of neurotransmitter function within the brain is becoming possible.

The combination of pharmacological challenges and fMRI (pharmacMRI or pMRI) has the potential to detect 5-HT effects on brain function. Recently, we demonstrated that infusion of the 5-HT_{2C} receptor agonist methyl-chlorophenylpiperazine (mCPP) provoked regional increases in BOLD signal corresponding to brain areas rich in 5-HT_{2C} receptors (Anderson et al. [2002](#); Marazziti et al. [1999](#)). Furthermore, responses in the hypothalamus correlated with subsequent prolactin secretion suggesting that the hypothalamic changes were functionally significant. We have termed drug-evoked changes in BOLD responses direct pMRI to distinguish it from the more widespread indirect pMRI methodology in which drug modulation of cognitive task-evoked BOLD responses is investigated. We showed indirect pMRI effects of mCPP in enhancing activation of lateral orbitofrontal cortex during the go/no-go tests, a motor inhibition task (Anderson et al. [2002](#)).

In this project, we extended our investigation of 5-HT pMRI by examining the effects of intravenous administration of the selective 5-HT reuptake inhibitor, citalopram, as a pharmacological challenge. Citalopram is an effective antidepressant and anxiolytic (Bakker et al. [2000](#); Keller [2000](#)). Single doses of citalopram increase 5-HT release by inhibiting the reuptake of 5-HT. This has been detected in experimental animals using intracerebral dialysis in hippocampus, frontal cortex and caudate nucleus (Hervás et al. [1998](#)). In humans, intravenous citalopram (5–10 mg) has been developed as probe of central 5-HT function by measuring increased prolactin secretion following its administration (Seifritz et al. [1996](#); Attenburrow et al. [2001](#)). We used similar doses to determine whether pMRI could detect and localise functional 5-HT effects in human brain. We hypothesised that citalopram would affect the BOLD response in brain areas known to be implicated in depression and in its response to antidepressants. These areas include the ventral cingulate and medial prefrontal cortex, amygdala, hippocampus, striatum and thalamus. Several of these areas were also responsive to mCPP in our previous study (Anderson et al. [2002](#)).

Materials and methods

Subjects

Twelve healthy male volunteers aged 19–36 years (mean±SD 24.7±5.8 years) participated. The study was approved by the local research ethics committee, and written informed consent was obtained from each volunteer. Psychiatric diagnoses

were excluded using the Overview Module from Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-NP; Spitzer et al. [1992](#)) and the Mini International Neuropsychiatry Interview (MINI; Sheehan et al. [1998](#)). Other exclusion criteria included any serious general medical condition or one that could interfere in the interpretation of results, use of medication within the last 2 weeks, illicit drug use, excessive consumption of alcohol (>21 units/week), caffeine (greater than eight cups of coffee per day) or cigarette (greater than ten cigarettes per day) and involvement in concurrent research or in research involving taking an experimental drug in the previous 2 months.

Pilot study

The dose and timing of the citalopram infusion were determined in a pilot study carried out on six male volunteers aged between 28 and 47 years evaluated twice in a single-blind crossover design with citalopram and placebo. The infusion was given, using a syringe driver, 45 min after cannulation. Blood samples (prolactin, cortisol and citalopram levels) were taken at 15-min intervals from 15 min before to 90 min after the drug infusion. Expected drug effects and mood changes were assessed using 100-mm visual analogue rating scales (VAS) (0 mm=not at all to 100 mm=extremely) for sad, anxious, panicky, lightheaded, happy, drowsy, nauseated and irritable. These were given 5 min before infusion, at time of infusion and every 2 min until 10 min after the infusion. Thereafter, VAS was given 15 min after the infusion and every 15–90 min. Initially, four volunteers received 5 mg of citalopram over 5 min diluted in 30 ml of saline. As no side effects were observed, the dose was increased for the two last volunteers to 7.5 mg diluted in 45 ml of saline solution over 7.5 min. This dose produced mild subjective effects but was well tolerated and therefore it was selected for the main study.

Procedures

Subjects were tested on two occasions, once with placebo (normal saline) and once with intravenous citalopram 7.5 mg, infused over 7.5 min, separated by at least 3 days (range 3–28 days, mean \pm SD 11.1 \pm 6.9 days), in a randomised, balanced order, single-blind design. Subjects were cannulated outside the scanner at least 30 min before they received the drug. They then underwent a 22.5-min fMRI scan. The drug was infused during the middle 7.5 min in order to examine the direct effects of citalopram, as shown in Fig. [1](#). A brain volume was obtained every 5 s. Subjects received Likert-type rating scales relating to possible drug side effects presented on a screen at 2.5-min intervals during the infusion scan and at 15-min intervals at other times. Subjects responded with a button press to a four-point scale (1—not at all, 2—slightly, 3—moderately, 4—extremely) for the following states: alert, anxious, calm, cold and clammy, comfortable, nauseous, drowsy, light-headed, sweaty, uncomfortable. Blood samples for prolactin, cortisol and citalopram were collected 20 and 15 min before the start of the drug infusion and every 15 min after over the next 2 h. Plasma prolactin concentrations were determined by immunoradiometric assay, cortisol by double antibody radioimmunoassay and citalopram by HPLC.

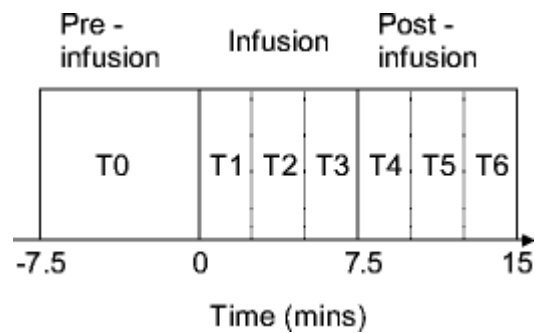


Fig. 1 The 22.5-min scan was divided into three 7.5-min sections (pre-infusion, infusion and post-infusion). T0 was the pre-infusion scan and included all 90 volumes in the 7.5-min time bin. The infusion and post-infusion scans were divided into three lots of 30 scan time bins (2.5 min each). T1–T3 were the time bins during infusion and T4–T6 were time bins post-infusion

fMRI scanning

Images were acquired using a Philips (Eindhoven, Holland) 1.5-T Gyroscan ACS NT. T2*-weighted volumes were acquired using a single-shot echo-planar (EPI) pulse sequence. Each volume comprised 40 contiguous axial slices (TR=5 s, TE=40 ms, 3.5-mm thickness with an in-plane resolution of 3×3 mm). A T1-weighted structural scan was also acquired for each subject for co-registration and to exclude any structural abnormality. No abnormalities were reported for any of the 12 subjects.

Statistical analysis

Statistical analyses of behavioural, hormonal and drug data were analysed using SPSS 10. Plasma hormone responses and subjective ratings were analysed as change from baseline using a repeated measure ANOVA with Huynh–Feldt correction and post hoc paired *t*-tests. Baseline-corrected areas under the curve (AUC) were calculated as indices of individual hormone responses and drug concentrations. The mean AUC were compared with paired *t*-tests.

Imaging data were analysed using Statistical Parametric Mapping (SPM2, Friston, The Wellcome Department of Cognitive Neurology, London, UK), with a random effects model. Images were realigned to correct for motion. These realigned images were then spatially normalised and smoothed to facilitate intersubject averaging.

First-level analysis was performed on each subject for placebo and citalopram infusion in the following way. As shown in Fig. 1, the 270 infusion scans were divided into seven time bins. The first time bin (T0) consisted of 90 pre-infusion scans (7.5 min). The next six time bins were each 30 scans in length (2.5 min), three during the infusion (T1, T2, T3) and three during post-infusion (T4, T5, T6). In each subject, these six infusion time bins were separately compared to T0 using regression analysis. This first-level analysis resulted in six first-level images (Tn–T0) corresponding to each time bin for each subject. To determine whether statistically significant increments in the voxels across subjects occurred following citalopram, a second-level (between-subject) analysis was carried out. Paired *t*-tests were used to compare first-level images after placebo and citalopram at each time bin.

In total, six paired t -tests (citalopram vs placebo) were computed showing areas of significance for each time bin (T_n). A threshold of $p < 0.001$ uncorrected was used for pre-hypothesised areas. Areas above this uncorrected threshold are also included in the results for interest but are not discussed further.

Results

Psychological effects

Only five of the 12 subjects had mild-moderate subjective effects following citalopram with only one yielding a clear time course of VAS changes. This was essentially a 40-s delayed linear increase during drug infusion reaching a plateau at 130 s after the start of infusion followed by a linear decrease to half the maximum height by the end of the scan. No statistical differences were obtained in the comparison of items of the VAS.

Citalopram levels

Average citalopram plasma levels increased, as shown in Fig. [2a](#). Peak concentrations occurred at 15 min post-infusion with the plasma level reducing after 30 min then plateauing for the subsequent 2 h.

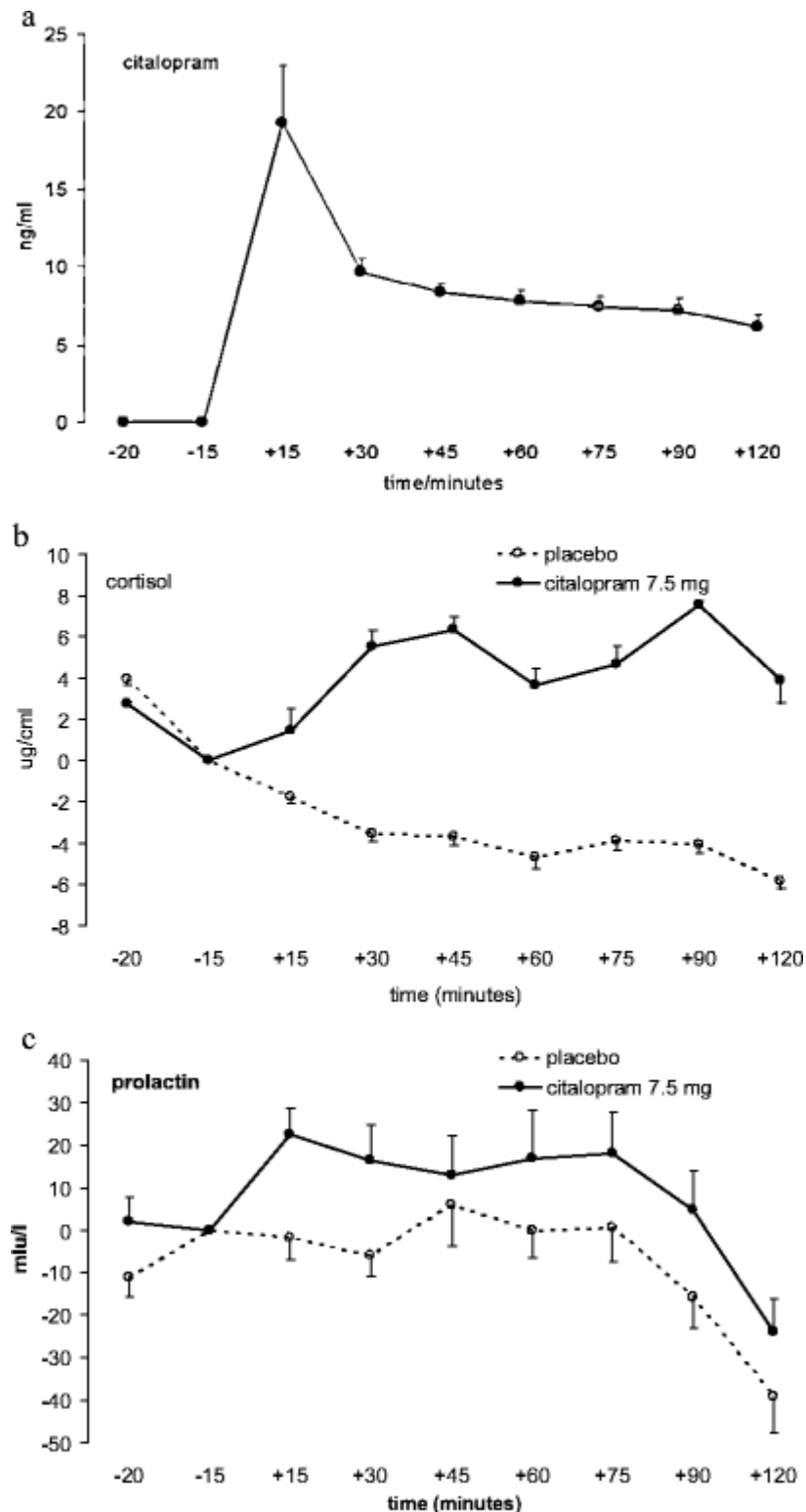


Fig. 2 Plasma citalopram concentrations and hormonal responses in 12 volunteers tested twice, under placebo or under intravenous citalopram (7.5 mg over 7.5 min) in a crossover design. **a** Mean \pm SEM plasma citalopram levels following citalopram infusion. **b** Mean \pm SEM plasma cortisol measured as a change from baseline (time=zero). Mean \pm SEM plasma prolactin measured as a change from baseline (time=zero)

Hormone measures

Citalopram increased hormone secretion, as shown in Fig. 2b and c, with a significant interaction between group and time in cortisol response [$F(3.78, 41.63)=6.99$; $p<0.001$]. There was a significant difference between conditions in the prolactin response [$F(1.00, 58.78)=7.59$; $p=0.019$] with prolactin levels being consistently higher under the infusion drug condition than under placebo from 15 min after the start of the infusion; however, no significant interactions between drug and time were detected in the prolactin responses [$F(5.34, 58.78)=1.97$; $p=0.322$]. Post hoc analyses showed significant differences in prolactin ($t=-2.40$; $p=0.035$) and cortisol ($t=-4.39$; $p=0.001$) AUC.

Pharmacological neuroimaging

Two comparisons (citalopram minus placebo and placebo minus citalopram) were calculated for each time bin (Tn) using a random-effects paired t -test. The results of these comparisons are summarised in Tables 1 and 2.

Table 1 Areas of significant activation following i.v. citalopram

Area	BA	Side	T1 coords	T2 coords	T3 coords	T4 coords	T5 coords	T6 coords
Superior frontal gyrus	6	R					18 6 66	15 6 66
		L						-21 6 63
	8							0 18 54
	9	R		30 48 39			15 36 45	12 36 45
Medial frontal gyrus	6	L						-3 -18 72
Middle frontal gyrus	6	R		30 9 69				
	8	L						-36 18 51
Inferior frontal gyrus	47	R					36 15 -21	48 39 -18
		L			-45 39 -15	-39 42 -15		-42 39 -15
Superior temporal gyrus	38	R					39 9 -33	
		L		-33 9 -33			-27 12 -24	-27 12 -33
	22	R					66 0 3	66 0 3
Middle temporal gyrus	21	R				54 3 -33	54 3 -30	
		L	-51 -21 -18			-66 -51 -6		
Inferior parietal lobe	40	R		45 -45 39				
Superior occipital	19	L		-39 -				

Area	BA	Side	T1 coords	T2 coords	T3 coords	T4 coords	T5 coords	T6 coords
gyrus				81 33				
Fusiform gyrus	37	L			-45 -60 -15			
Cuneus	18				0 -102 3			
Anterior cingulate	32							0 36 -3
	25	L			0 18 -9	-3 15 - 9	-3 12 - 12	-3 15 - 12
Cingulate gyrus	23	L						-6 -12 27
Caudate		R					12 12 18	9 6 21
		L			-18 21 9	-12 15 6	-15 15 3	-15 18 9
Parahippocampal gyrus	34 Amyg	R			12 3 - 21	30 0 - 18	15 3 - 21	
	28	L					-18 -9 -24	-15 -12 -24
Uncus	34	R					18 0 - 24	
	28	R					30 3 - 24	
		L					-24 3 - 33	
Thalamus		L						-3 -6 - 3
Brainstem	Pons	R						3 -9 - 24

Significant voxels ($p < 0.001$; $z > 3.07$) for the six paired t -tests comparing citalopram minus placebo in 12 subjects for each time bin. Z-scores are omitted for clarity: they all lie between 3.08 and 4.17. Column 1 is the area description. Column 2 identifies the relevant Brodmann areas. Column 3 identifies the side of the response—left or right hemisphere. Columns 4–9 locate each cluster of significantly activated voxels in MNI coordinates [x, y, z (in mm)]

Table 2 Areas of significant deactivation following i.v. citalopram

Area	BA	Side	T1 coords	T2 coords	T3 coords	T4 coords	T5 coords	T6 coords
Middle frontal gyrus	6	R	42 -3 54					
Inferior frontal gyrus	44	R			51 12 21			
Precentral gyrus	44	R			51 9 12			
Postcentral	2	R				57 -24		

Area	BA	Side	T1 coords	T2 coords	T3 coords	T4 coords	T5 coords	T6 coords
gyrus						57		
Lingual gyrus	18	L					-18 -75 -3	
Cerebellum		R	3 -48 - 18					

Significant voxels ($p < 0.001$; $z > 3.07$) for the six paired t -tests comparing placebo minus citalopram in 12 subjects for each time bin. Z-scores are omitted for clarity but lie between 3.15 and 4.35. Column 1 is the area description. Column 2 identifies the relevant Brodmann areas. Column 3 identifies the side of the response—left or right hemisphere. Columns 4–9 locate each cluster of significantly activated voxels in MNI coordinates [x, y, z (in mm)]

Citalopram minus placebo

Several areas showed significant effects of time for citalopram minus placebo. The superior frontal gyrus (BA6 bilaterally, BA8 and right BA9) was significant in T5 and T6, as was the left middle frontal gyrus (BA8) and the superior temporal gyrus (BA38 bilaterally and right BA22). There were bilateral increases in the inferior frontal gyrus (BA47); however, left was significant at T3, whereas the right was significant later at T5. There were also a bilateral increases in the middle temporal gyrus (BA21) at the early stages of post-infusion (T4 and T5). Occipital and parietal activations were significant at T2 and T3: these included the right inferior parietal lobe (BA40), the left superior occipital gyrus (BA19), the left fusiform gyrus (BA37) and the cuneus (BA18). Activations in left anterior cingulate (BA25) were significant from T3 until T6, as was the left caudate as shown in Figs. 3 and 4. The right caudate was significant during T5 and T6. Activations in left and right caudate occurred in the same time bins as left and right inferior frontal gyri. Significant increases at T6 were also observed in the right anterior cingulate (BA32) and the left cingulate gyrus (BA23). From T3 to T5, the right amygdaloid complex (BA34) was significant. This area includes the parahippocampal gyrus, the amygdala and the uncus. The left amygdaloid complex (BA28) was significant in T5 and T6. Activations were observed in the left thalamus and the right brainstem at T6.

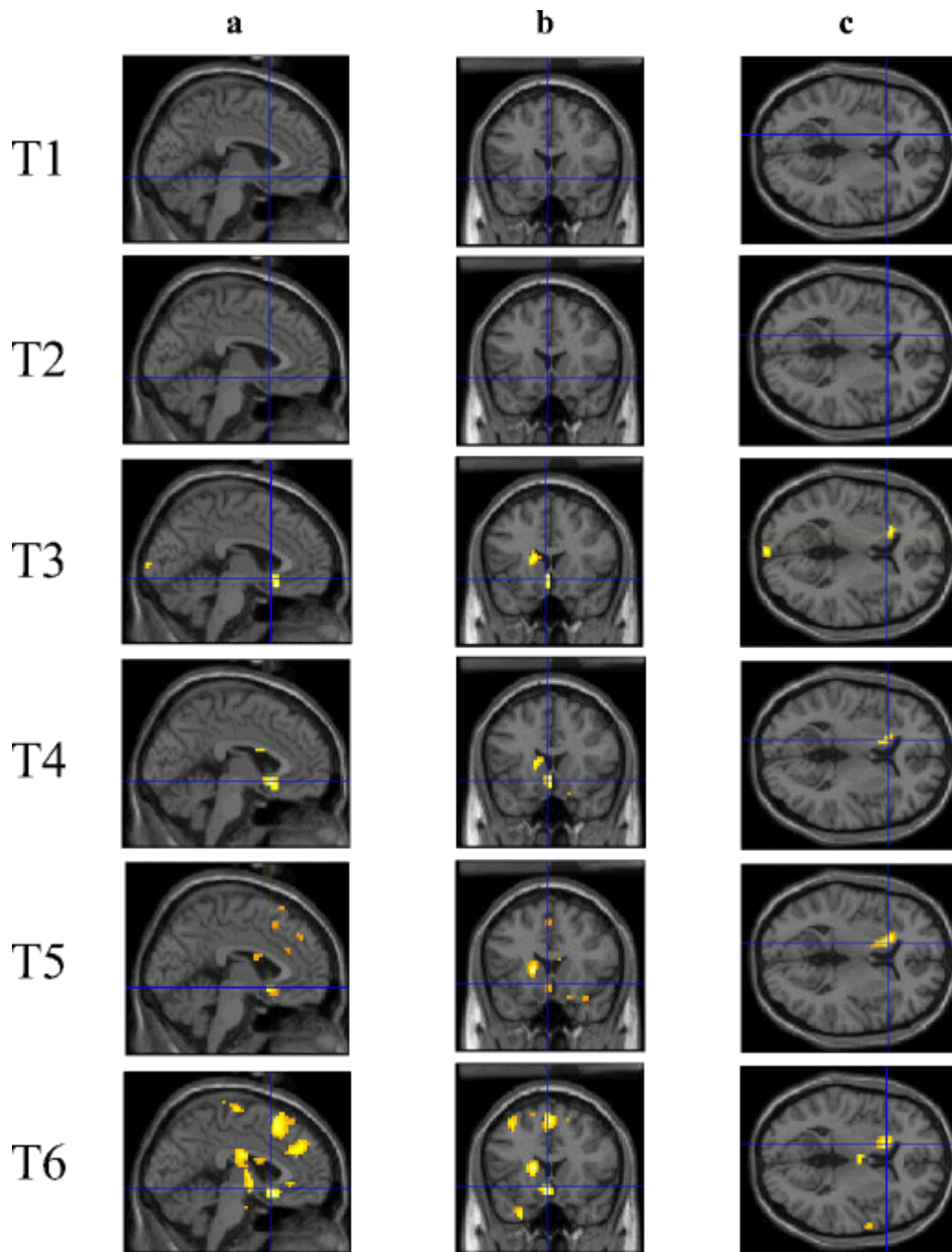


Fig. 3 Areas of significant activation following i.v. citalopram in successive 2.5-min blocks from onset of infusion (T1) to T6 12.5–15 min after onset of infusion. Statistically significant areas for each time bin for 12 volunteers using a random-effects paired *t*-test for citalopram minus placebo infusion. **a** Sagittal sections showing left anterior cingulate (BA25, $-3\ 15\ -9$). **b** Coronal sections showing left anterior cingulate (BA25) and the left caudate activations. **c** Horizontal sections showing left caudate ($-15\ 18\ 6$). Both areas can be seen to be expanding in size and significance with time after infusion. Other areas become significant during the T5 and T6 time bins

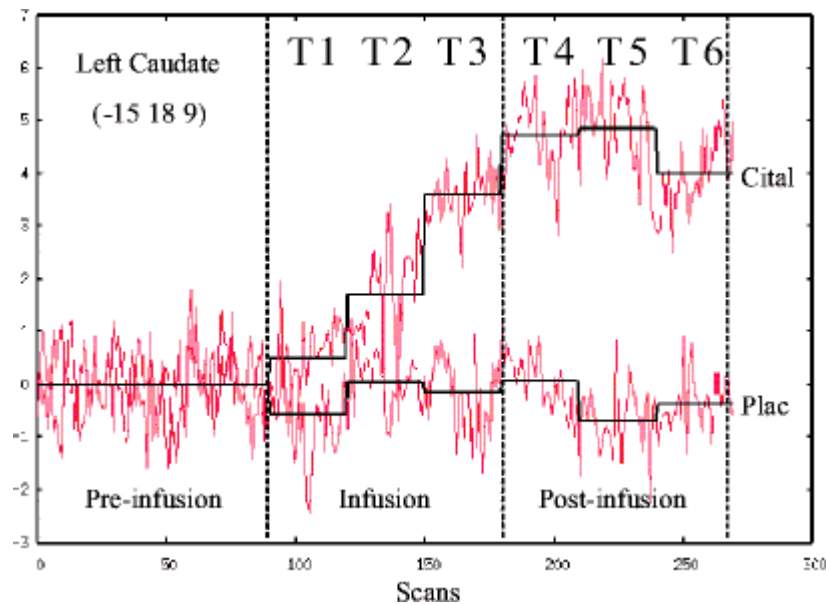


Fig. 4 Citalopram and placebo time series are shown with the mean values in successive 2.5-min bins shown in *black*

Placebo minus citalopram

There were no obvious patterns in the placebo minus citalopram subtraction with no area remaining significant for longer than one time bin. The areas of significance included the right middle temporal gyrus (BA6), the right inferior frontal gyrus (BA44), the right precentral gyrus (BA44), the right postcentral gyrus (BA2) and the left lingual gyrus (BA18).

Discussion

The method of analysis reported in this paper would appear to have been successful in modelling the BOLD signal changes across the brain that are due to citalopram infusion.

Various methods have been applied to analyse pMRI data in the past; these include a pharmacokinetic regressor (Wise et al. [2002](#)) and a regressor based on visual analogue scales (VAS) (Anderson et al. [2002](#)). The primary disadvantage with these methods is that they are not effective at modelling latency effects since they assume that all areas show BOLD signal increases at the same time. Using VAS carries the additional uncertainty that only brain regions mediating subjective effects are identified, whereas others unrelated to subjective effects are not.

Similar methods to that employed in this study have been used in the past. Shoaib et al. ([2004](#)) used a simple comparison between pre- and post-infusion in the nucleus accumbens in rats. The method in this paper has the advantage of having more temporal resolution and spatial extent. Houston et al. ([2001](#)) used a running average of pixels and compared to an equivalent baseline running average with a *t*-test. This

method is the most similar to our method and does not appear to have any latency or spatial disadvantage.

Independent component analysis (ICA) (Himberg et al. [2004](#); Schmithorst and Holland [2004](#)) has been used to model fMRI data without prior hypotheses of the signal being investigated. Calhoun et al. ([2004](#)) used the method to investigate alcohol effects but in an indirect paradigm observing modulation of responses evoked by a driving task. We will compare ICA with the method used here in future studies.

The predominant response to citalopram was activation. The gradual buildup of responses with no areas of activation appearing before expected subjective effects or peak plasma levels offers some validation that the changes are true biological drug effects. Areas of deactivation did not show consistent changes over time. One possibility is that reduction in neuronal function from a resting state is not associated with reduced flow sufficient to alter the local proportion of oxygenated to deoxygenated haemoglobin—the basis of the BOLD response. 5-HT has important influences on cerebral vasculature which might contribute to the activations seen, and there is also the theoretical possibility that citalopram may have altered blood flow through changes in blood pressure. An argument against this is that citalopram has not been reported to alter cardiovascular parameters when given in higher doses in humans (Seifritz et al. [1996](#); Penttila et al. [2001](#)), and the activations were focal and not obviously related to known vascular patterns. Furthermore, McBean et al. ([1999](#)) showed that the effects of acute citalopram administration on local changes in blood flow in rats were tightly linked to local changes in regional glucose metabolism. They concluded that direct effects of 5-HT release on the vasculature would have produced changes in flow independent of changes in metabolism.

Activations were seen in areas implicated in the pathogenesis of depression and in treatment-induced recovery. Notably, subgenual cingulate gyrus showed sustained activation beginning shortly after the infusion. Studies using positron emission tomography (PET) to image resting regional blood flow have reported subgenual cingulate overactivity in patients with depression and normalisation with recovery (Mayberg et al. [2000](#)). Imaging studies in depression also report altered flow or metabolism in amygdala, caudate and ventral frontal cortex (see Drevets [2000](#)). In each of these regions, citalopram pMRI activations were seen, and they were also activated in our study of mCPP, a 5-HT_{2C} agonist (Anderson et al. [2002](#)). These regions express high levels of 5-HT_{2C} receptor protein (Clemett et al. [2000](#)) which are thought to have excitatory effects on GABA neurones (Lee et al. [1999](#)). We therefore hypothesise that activations in caudate, cingulate and amygdala are mediated by 5-HT_{2C} receptors. We further predict that these activations will attenuate with repeated treatment because 5-HT_{2C} receptors undergo marked desensitisation by agonists and during antidepressant treatment (Devlina et al. [2004](#); Zohar et al. [1988](#)). 5-HT_{1A} receptors hyperpolarise pyramidal cells in cortex and hippocampus and deactivations were expected, especially in hippocampus. Instead, frontal cortical and hippocampal activations were observed. It is possible that initial silencing of 5-HT cells via cell-body autoreceptors may outweigh terminal uptake inhibition producing a transient decrease in 5-HT release in some regions. It is difficult to specify which regions because the immediate effects of citalopram on terminal 5-HT release are a complex function of autoreceptor distribution in the raphe and the relative local preponderance of terminal autoreceptors and uptake sites. With repeated treatment,

autoreceptors are thought to desensitise allowing large increases in terminal 5-HT to occur by reuptake inhibition. Thus, some of the positive BOLD responses seen immediately after i.v. citalopram might reverse direction with chronic treatment. Immediate responses might therefore locate key initial sites of action of citalopram, but the direction of change may not be the same as that which ultimately mediates antidepressant effects. Further work is necessary to understand these changes, and studies with selective antagonists should assist in identifying the receptor basis of citalopram pMRI.

In conclusion, we have developed a method of detecting the central effects of acute citalopram administration to normal volunteers. BOLD responses emerging over 15 min after the onset of citalopram infusion were seen in caudate, subgenual and anterior cingulate, amygdala, hippocampus and frontal cortex. These regions have been implicated in the mechanisms of action of antidepressants. Direct pMRI using i.v. citalopram opens new ways of investigating 5-HT mechanisms in depression and its treatment. The method described could be applied to other 5-HT challenge drugs provided they can be administered rapidly and safely intravenously.

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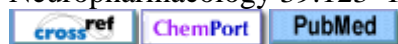


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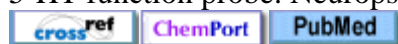
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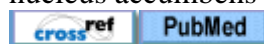


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