

Effect of the 5-HT_{1A} partial agonist buspirone on regional cerebral blood flow in man

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Abstract. Repeated measurements of regional cerebral blood flow (rCBF) were made in normal volunteers before, and after, the administration of the 5-HT_{1A} partial agonist, buspirone, or placebo. The difference in rCBF, before and after drug, (buspirone versus placebo) was used to identify brain areas affected by buspirone. Buspirone-induced changes in rCBF were studied under two behavioural conditions (5 word-list learning and 15 word-list learning). Compared to placebo, buspirone increased blood flow in the cuneus during both behavioural states. However, decreases in blood flow, centred in the left dorso-lateral prefrontal cortex and posterior cingulate cortex, were only observed under one of the two behavioural conditions. It is concluded that buspirone-induced alterations in regional cerebral blood flow are better understood, not in relation to the known distribution of monoamine neurotransmitter systems (particularly ascending 5-HT projections), but rather in relation to putative neuronal circuits possibly many synapses “downstream” of buspirone’s pharmacological site of action.

Key words: Buspirone – 5-HT_{1A} receptors – Positron emission tomography – Statistical parametric mapping – Pharmacological challenge

Buspirone, an azaspirodecanedione, is a novel anxiolytic and antidepressant which binds with nanomolar affinity to the 5-HT_{1A} receptor and has functional properties of a 5-HT_{1A} partial agonist (Peroutka 1985; Traber and Glaser 1987; Robinson et al. 1990). It has been proposed that the anxiolytic effects of buspirone are mediated via changes in 5-HT neurotransmission – putatively a reduction in 5-HT neurotransmission through activation of 5-HT_{1A} autoreceptors. In addition to this, however, buspirone acts on 5-HT_{1A} receptors postsynaptic to 5-HT

neurones (Traber and Glaser 1987). Buspirone also increases dopaminergic and noradrenergic neurotransmission possibly through antagonism of presynaptic dopamine D₂ receptors (McMillen et al. 1983; Eison and Temple 1986; Fuller and Perry 1989) and the alpha₂ adrenoceptor antagonist properties of its active metabolite, 1PP (Caccia et al. 1986; Bianchi and Garattini 1988; Gobbi et al. 1990). Despite considerable experimental data on buspirone’s effects in animals, little is known about the brain areas targeted functionally by buspirone in humans. One approach that may prove useful in understanding the central effects of pharmacological agents in man is the use of positron emission tomography (PET) or single photon emission tomography (SPET) techniques to measure drug induced changes in regional cerebral blood flow (rCBF) (for example, see Geaney et al. 1990; Jones et al. 1991). Cerebral blood flow measurement is, under most circumstances, a valid index of neuronal activity in vivo and in addition, is sensitive to physiological/behavioural challenges (McCulloch 1982; Raichle 1987; Posner et al. 1988).

Using positron emission tomography we report the effects on rCBF of a single oral dose of buspirone in normal volunteers. Our aims were to determine 1) the brain areas altered by buspirone administration (as indexed by changes in rCBF) and 2) whether the pattern of rCBF changes was understandable in the context of the known neuroanatomy of transmitter systems influenced by buspirone.

Materials and methods

Subjects. A total of 12, right-handed, male volunteers (age range 25–36 years) took part in the study which was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee on the Administration of Radioactive Substances (ARSAC) UK.

Drug administration. Each subject underwent six PET measurements of rCBF over a 80 min period. Two measurements of rCBF were undertaken before ($t = -12$ min, -2 min), and four measure-

ments after ($t = +25$ min, $+35$ min, $+55$ min and $+65$ min) buspirone 30 mg orally or placebo. Scan times post buspirone were chosen on the basis of buspirone kinetics and the induction of centrally mediated neuroendocrine responses. Buspirone kinetics show a time to maximum plasma concentration of 0.78 h following buspirone 20 mg orally (Gammans et al. 1986). Plasma neuroendocrine responses (prolactin and growth hormone increases) begin approximately 30 min following buspirone 30 mg orally and reach a maximum at 65–75 min (Anderson and Cowen 1992). Subjects were blind to the drug administered. Six subjects received buspirone, six subjects received placebo.

Experimental design. Subjects performed auditory-verbal memory tasks with eyes closed during PET scanning. Such standardisation of behavioural state allows for a reduction in intra- and inter-subject variability in rCBF. Two distinct memory tasks were used; a subspan task (immediate recall of five-word lists) during the first, third and fifth scan and a supraspan task (immediate recall of 15-word lists) during the second, fourth and sixth scan. We chose to study subjects under two behavioural states so that interactions between drug effects on rCBF and behavioural state could be examined. Buspirone or placebo was given after the second scan. The experiment, as designed, allowed for the examination of three effects on rCBF. These were (1) the simple main effects of buspirone under each behavioural state, (2) the simple main effect of the supraspan-subspan memory tasks (before/after buspirone) (3) buspirone-memory task interactions. In this paper the simple main effects of buspirone are reported. The effect of the supraspan-subspan memory challenge and buspirone-memory interactions will be reported separately (see Friston et al. 1991c for preliminary report).

PET scanning. Scans were obtained using a CTI model 931–08/12 PET scanner (CTI, Knoxville, TN, USA). The physical characteristics of this scanner system have been described previously (Spinks et al. 1988). Scans were reconstructed using a Hanning filter with a cut off frequency of 0.5 giving a transaxial resolution of 8.5 mm full width at half maximum and an axial resolution of 6.75 mm for each of 15 transverse planes with a resulting total field of view of 10.13 cm in this direction.

Subjects inhaled trace amounts of $C^{15}O_2$ mixed with air at a concentration of 6 MBq/ml and a flow rate of 500 ml/min through a disposable oxygen face mask for a period of 2 min. Two PET scans were collected over a period of 2.5 min beginning 0.5 min before the inhalation of $C^{15}O_2$ (background scan duration 0.5 min, second scan duration 2.0 min) (adapted from Lammertsma et al. 1990). In this study, the integrated counts per pixel for the two minute build-up phase of radioactivity in the brain during $C^{15}O_2$ inhalation were used as an index of rCBF (Fox and Mintun 1989).

Measurement of plasma prolactin, growth hormone and buspirone. To obtain evidence (independent of rCBF changes) for an effect of buspirone on central monoamine systems, four measurements of plasma prolactin and growth hormone were obtained from blood drawn from an in-dwelling venous cannula ($t = -20, 0, 20$ and 40 min post-buspirone). Prolactin and growth hormone were measured by radioimmunoassay as described previously (Cowen et al. 1985). Plasma buspirone concentrations were measured at $t = -20, 0, 20$ and 40 min post-drug using high performance liquid chromatography with coulometric detection (Franklin 1990).

Measurement of side effects of buspirone administration. To assess the potential confounding effect on rCBF of buspirone induced side-effects all subjects were assessed on three occasions ($t = -7$ min pre-buspirone/placebo, $+30$ min and $+60$ min, post-buspirone/placebo) for levels of arousal and stress on a 24-item questionnaire (Mackay et al. 1978) and in addition subjects rated nausea, light-headedness and drowsiness on visual analogue scales.

Data analysis. Each reconstructed rCBF scan consisting of 15 primary transverse planes was interpolated to 43 planes to render the voxels approximately cubic. The data were then transformed into

a standard stereotactic space (Friston et al. 1989, 1991b). Such transformation of the data allows for pixel by pixel averaging of data across subjects. In the standard space 1 voxel represents $2 \times 2 \times 4$ mm in the x, y and z dimensions, respectively, allowing direct cross reference to the anatomical features in a standard stereotactic atlas (Talairach and Tournoux 1988). A Gaussian filter 10 pixels wide was applied to smooth each image to account for inter-subject differences in gyral and functional anatomy and to suppress high frequency noise in the images.

Differences in global activity within and between subjects were removed by analysis of covariance (Wildt and Ahtola 1978) on a pixel by pixel basis with global counts as covariate and regional activity across subjects for each task as treatment. This procedure was undertaken as inter- and intra-subject differences in global activity may reduce the likelihood of detecting regional alterations in blood flow following activations (Friston et al. 1990).

For each pixel, in stereotactic space, the analysis of covariance generated six condition-specific (i.e. scans 1–6) mean rCBF equivalent values (normalised to 50 ml/dl/min) and an associated error variance. The changes of interest were rCBF changes attributable to buspirone that were statistically greater than those induced by placebo. This represents an interaction (pre-drug versus post-drug \times placebo versus buspirone). This interaction term was computed using the *t*-statistic (with appropriate contrast and adjusted error variance). The error variance was computed independently for the placebo and buspirone studies using a completely randomized block design ANCOVA and the average from the studies used. The resulting set of *t* values constitutes a statistical parametric map [SPM(*t*)] (Friston et al. 1991a). With so many comparisons being made, many *t* values will reach conventional levels of significance by chance. Therefore the “omnibus” significance of the SPMs was assessed, using the Chi-Square statistic, by comparing the expected and observed number of *t* values which exceeded a threshold of $P < 0.001$. If this statistic was significant (for a given contrast) the location of all pixels with a *t* value corresponding to $P < 0.001$ was used to define the profile of buspirone-induced rCBF changes compared to placebo. The results presented are rCBF data from the pre-drug scan (1 or 2) compared to post-drug scans (3 + 5 or 4 + 6), buspirone compared to placebo. Because of the smoothing function used (see above) the final individual values for rCBF at any one pixel represent blood flow in a weighted spherical domain of about 20 mm diameter.

Image analysis was performed using SPM software (MRC Cyclotron Unit, London, UK) on a SPARC 1 workstation (Sun Microsystems Inc, Surrey, UK) using an interactive image analysis software package (ANALYZE), Biodynamic Research Unit, Mayo Clinic, USA). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc, New York).

Results

The study design allows for drug induced alterations in regional brain activity (measured as rCBF equivalents) to be determined. Buspirone-induced changes in rCBF represent relative increases or decreases compared to placebo. It should be noted that increases and decreases of rCBF may also have occurred outside the axial field of view of the scanner.

*Observed and expected distribution of *t* statistic in post-drug versus pre-drug comparisons, buspirone versus placebo*

There was a significant difference in the observed and expected distribution of the *t* statistic (at the threshold of

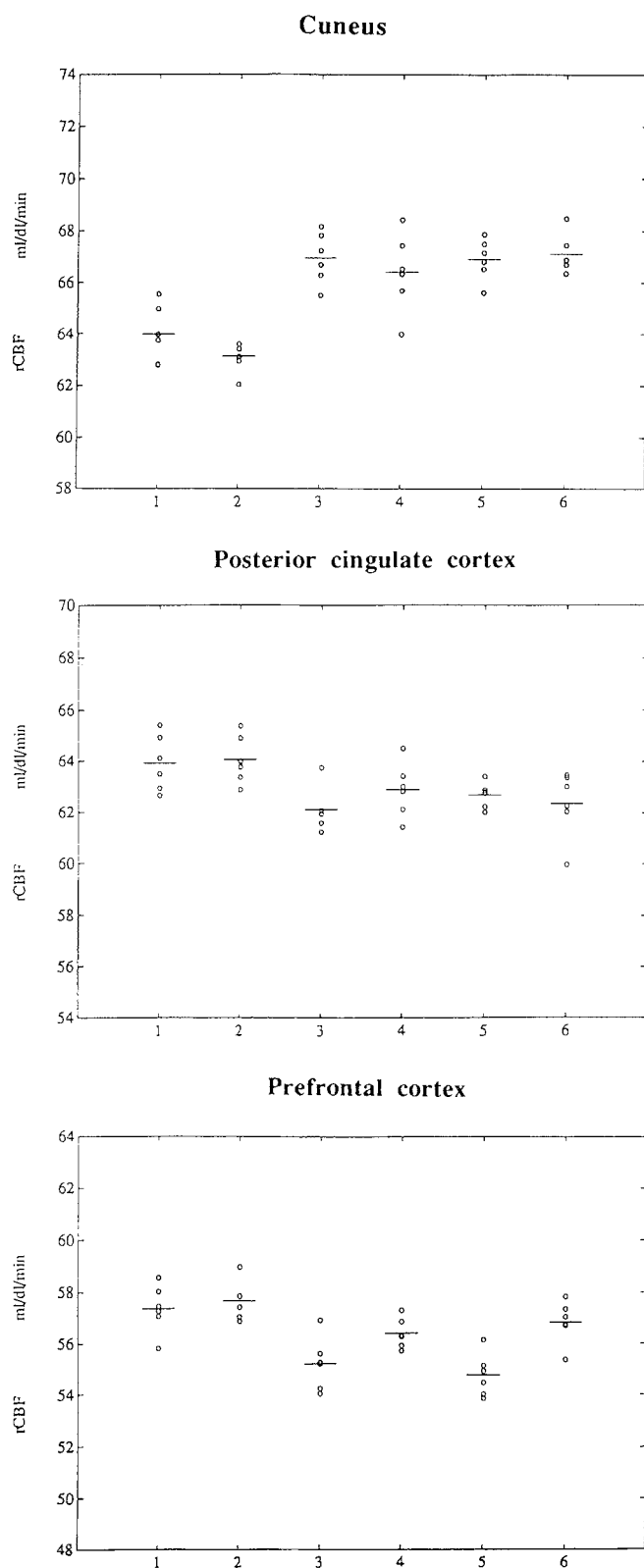


Fig. 1. rCBF changes in the cuneus, posterior cingulate cortex and left prefrontal cortex (buspirone condition). Values on ordinate are cerebral blood flow equivalents (ml/dl/min) for individual subjects, normalised to a global blood flow of 50 ml/dl/min, at the co-ordinates specified in Table 1. *Open circles* refer to individual values for rCBF, *horizontal bars* refer to mean values. The *abscissa* refers to PET scan number. The 5 word list task was undertaken during scans 1, 3 and 5, the 15 word-list task during scans 2, 4 and 6. Buspirone was given after scan 2

$P < 0.001$) for buspirone-induced increases in rCBF under both behavioural tasks (Chi squared 196, df 1, $P < 0.0005$, Chi squared 325, df 1 $P < 0.0005$, 5 and 15 word-list conditions, respectively). In contrast, a significant difference in the observed and expected distribution of the t statistic, for buspirone-induced decreases in rCBF, was only seen under the behavioural state induced by five word-list learning (Chi squared 52, df 1, $P < 0.0005$).

Site of buspirone-induced increases in regional cerebral blood flow

Significant increases of regional cerebral blood flow were observed bilaterally in an area centred in the cuneus of the occipital cortex under both behavioural tasks (Table 1, Figs. 1, 2, 3).

Sites of buspirone-induced decreases in regional cerebral blood flow

Significant reductions in rCBF were seen in the left dorso-lateral prefrontal cortex and bilaterally in the posterior cingulate cortex but only under the condition of five word-list learning (Table 1, Figs. 1, 2, 3).

Plasma prolactin, growth hormone and buspirone following buspirone administration

There was a significant increase in plasma prolactin and growth hormone following buspirone administration ($t = -20$ min versus $t = +40$ min; prolactin 143 ± 103 versus 313 ± 152 mIU/l, growth hormone 3 ± 7 versus 17 ± 14 mIU/l, $P < 0.05$ Student's t -test). There were no significant increases in plasma prolactin or growth hormone following placebo. Plasma buspirone concentrations were 2.69 ± 2.51 ng/ml at $t = 20$ min and 2.56 ± 3.36 ng/ml at $t = 40$ min.

Stress, arousal and side effects of buspirone administration

Measures of stress and arousal decreased during the study in both buspirone and placebo treated groups (buspirone group; stress 18 ± 2 to 11 ± 0 , arousal -3 ± 2 to -7 ± 3 placebo group; stress 19 ± 2 to 14 ± 2 , arousal -1 ± 2 to -7 ± 3 , means \pm SD). Buspirone was well tolerated in all subjects. Side effects observed were mild in all cases. When side effects were reported, in most subjects, they were rated as present to some degree before drug administration. One subject reported a mild increase in nausea following buspirone, three subjects reported increased drowsiness, and four subjects a mild increase in light headedness. In the placebo group, two subjects reported mild increases in drowsiness and one subject an increase in light headedness (data not shown).

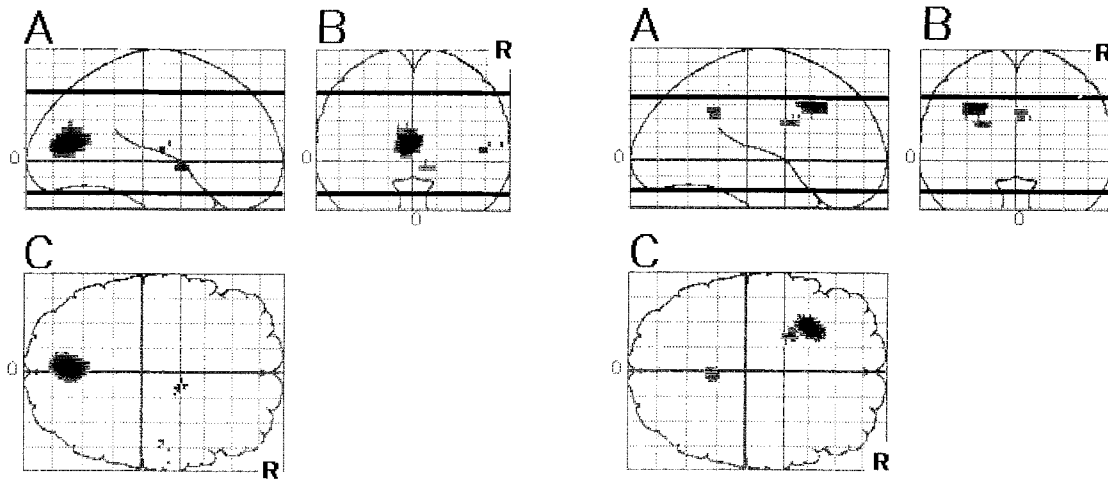


Fig. 2. Location of increases and decreases in rCBF. *Left images:* the spatial distribution of significant pixels at $P < 0.001$ for buspirone-induced increases in rCBF, compared to placebo. *Right images:* the spatial distribution of significant pixels at $P < 0.001$ for buspirone-induced decreases in rCBF compared to placebo. Images

are shown as integrated projections through sagittal (A), coronal (B) and transverse (C) views of the brain. R=right. The axial extent of the data set is indicated by thick lines in the sagittal (A) and coronal (B) views

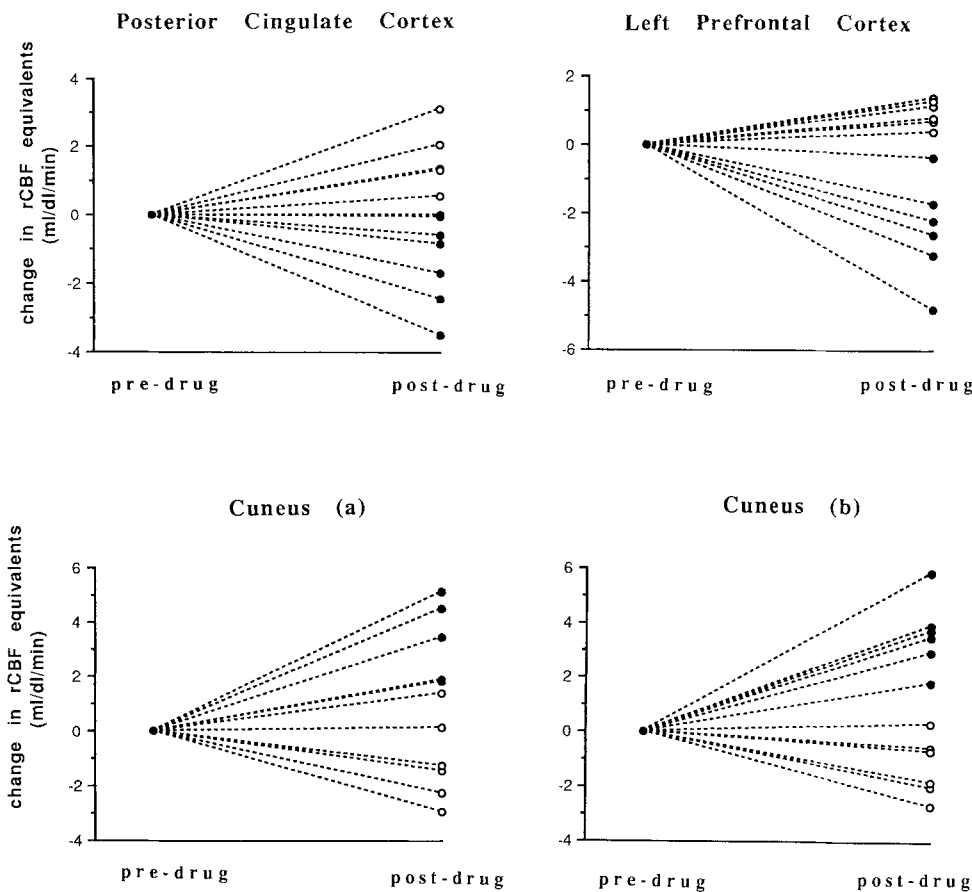


Fig. 3. rCBF changes in the left prefrontal cortex, posterior cingulate cortex and cuneus (post-drug vs pre-drug scans, buspirone compared to placebo). Values on ordinate are post-drug changes in cerebral blood flow equivalents (ml/dl/min) for individual subjects, normalised to pre-drug baseline, at the co-ordinates specified in Table 1. *Open circles* refer to placebo, *closed circles* to buspirone treatment. (a)= 5 word list task, (b)= 15 word-list task

Discussion

We have shown that the techniques of rCBF measurement, using integrated counts during the buildup phase of radioactivity following $C^{15}O_2$, and statistical parametric mapping enable the detection of significant, regionally discrete, “relative” changes in rCBF following a bus-

pirone challenge. It is unlikely that the changes in rCBF are due to a non-specific side effect of buspirone, as side effects were mild in all cases and similar decreases in stress and arousal occurred in buspirone and placebo groups. However, it should be noted that we cannot exclude the possibility that buspirone’s effects result from a direct action on cerebral blood vessels – particularly as

Table 1. rCBF equivalent values and stereotactic co-ordinates of maximal significant change following buspirone administration under two memory tasks

Anatomical location	Co-ordinates			Buspirone rCBF change	Placebo rCBF change
<i>Decreases in rCBF</i>					
	x	y	z		
Left Prefrontal Cortex (5-word condition)	-30	18	36	-2.47 ± 1.49**	0.95 ± 0.38
Posterior Cingulate (5-word condition)	2	-46	28	-1.53 ± 1.29*	1.39 ± 1.09
<i>Increases in rCBF</i>					
Cuneus (15-word condition)	-4	-80	8	3.63 ± 1.35**	-1.25 ± 1.11
Cuneus (5-word condition)	-6	-74	12	3.10 ± 1.47**	-1.08 ± 1.57

The stereotactic co-ordinates of maximal decreases and increases in rCBF are given in x, y, and z co-ordinates, from the atlas of Talairach and Tournoux. Values refer to rCBF equivalents from spherical regions of diameter 20 mm centred at the co-ordinates shown, results in rCBF equivalents, ml/dl/min, mean ± SD ** $P < 0.001$ Student's *t*-test (unpaired), * $P < 0.002$ Student's *t*-test (unpaired)

some 5-HT₁-like receptor agonists alter blood vessel diameter (Saxena and Ferrai 1989; Parsons 1991). Against this view, however, is the fact that the areas affected do not correspond to the territory of an individual cerebral vessel. In addition, in the rat, regional cerebral blood flow and glucose metabolism remain coupled following 5-HT_{1A} receptor stimulation (McBean et al. 1991). This would imply that 5-HT_{1A} receptor mediated changes in blood flow are secondary to changes in neuronal activity.

The pattern of rCBF change is not fully explained by the distribution of monoamine terminals or receptors. For example, although ascending 5-HT cortical projections have a high density in the occipital (visual) cortex of primates (Molliver et al. 1987), an area showing increased rCBF, other primary sensory areas with equivalently dense 5-HT projections were not activated by buspirone. The highly asymmetrical effect of buspirone on rCBF in the left dorsolateral prefrontal cortex (no reduction in rCBF was seen in the right dorsolateral prefrontal cortex even at a lower omnibus threshold of $P < 0.01$) is not mirrored by any reported lateralization of 5-HT projections in this area. As with the 5-HT system, a simple correspondence between buspirone-induced changes in rCBF and the distribution of ascending dopaminergic and noradrenergic neurotransmitter terminals or receptors (Parnavelas and Papadopoulos 1989; Berger et al. 1991) is difficult to demonstrate.

The location of buspirone-induced increases in rCBF was similar under both behavioural tasks. However, buspirone-induced decreases in rCBF were only detectable under one behavioural state (five word-list learning) at the chosen threshold of $P < 0.001$ in the statistical parametric map. The moderate differences in scan times in the comparisons (-12 min versus +25 and +55 min compared to -2 min versus +35 and +65 min) appear insufficient to explain this finding, especially as buspirone-induced increases of rCBF were detectable under both sets of scans. An alternative explanation is that there was an interaction between buspirone and rCBF changes induced by the 15 word-list task in certain brain

regions which thus "masked" any drug effect. Analysis of the effects of the word-list tasks on rCBF support this latter explanation as prefrontal and posterior cingulate cortex increases in rCBF were observed with the 15 word-list task (see Fig. 1 and Friston et al. 1991c, for preliminary report). These results suggest that the manifestation of central drug effects on integrated brain functional activity (indexed by rCBF) may be dependent on the brain state under which subjects are studied. McCulloch (1982) has stressed that functional mapping of drug effects is best understood in relation to neuroanatomical circuitry. Thus, it is possible that buspirone-induced changes in rCBF were initiated by alterations in monoamine neurotransmission but that neuronal circuits, downstream of the pharmacological site of action, were involved in the manifestation of rCBF changes. This explanation would be consistent with a putative neuromodulatory role for monoamine systems (Foote 1987) in diverse cortical functions organised as distributed neuronal circuits (Goldman-Rakic 1988; Mesulam 1990).

Mapping of central drug effects in normal volunteers with PET and SPET, when compared with rCBF profiles associated with psychiatric illnesses, might serve to implicate certain brain sites in psychotropic drug action. In the case of buspirone chronic, rather than acute administration, is associated with anxiolysis in humans. Therefore the brain areas identified in this study (prefrontal cortex, posterior cingulate and cuneus) may not necessarily be relevant to the anxiolytic effect of the drug. Furthermore, the profile of rCBF in anxious patients is unknown although some studies implicate the temporal poles (Reiman et al. 1989; Mathew and Wilson 1990). The left prefrontal cortex is known to be implicated in diverse higher cognitive functions that involve "willed" or internally generated behaviour (Frith et al. 1991) and in addition dysfunction of the dorsolateral prefrontal cortex has been linked to depressive illness (Baxter et al. 1989). In this regard, buspirone-induced reductions in left dorsolateral prefrontal blood flow mimic the changes in glucose metabolism and rCBF reported in patients with depressive illness (Baxter et al. 1989; Bench et al.

1991); a condition putatively linked to alterations of serotonergic and noradrenergic neurotransmission (for review see Caldecott-Hazard et al. 1991). Without further pharmacological characterization or challenge studies with other 5-HT_{1A} agonists, the pharmacological interpretation of our results must remain speculative. Despite this limitation, the discrepancy between buspirone-induced changes in rCBF and the distribution of monoamine systems, suggests that changes in rCBF may relate better to the modulation of activity in distributed neuronal circuits perhaps one or more synapses away from buspirone's pharmacological site of action. Furthermore, we suggest that drug challenge paradigms, in conjunction with the functional imaging and data analysis techniques described here, provide a potentially useful tool for examining the central effects of pharmacological agents in humans.

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