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Brain activation during an auditory 'oddball task' in schizophrenia measured by single photon emission tomography

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ABSTRACT

Background. The study examines the effect of an auditory discrimination task on regional brain perfusion in schizophrenic patients.

Methods. Twenty patients were examined with single photon emission tomography (SPET), both resting and performing an auditory two-tone 'oddball' discrimination task. Statistical parametric mapping (SPM'95) was used to identify local activation effects and correlations between event related potential measures and regional perfusion.

Results. Compared with rest, patients activated left superior temporal gyrus during the task, together with right caudate. There was a (negative) correlation between P300-amplitude and perfusion during the activation procedure in both caudate nuclei and in the left lingual gyrus. No correlations were observed with P300-latency. Compared with healthy volunteers examined in earlier studies, our patients showed no frontal activation. This might be due to slightly different task demands in this study, but more likely to activation-hypofrontality in schizophrenic patients compared with controls.

Conclusion. Auditory discrimination tasks can be used in schizophrenic patients to control their 'mental set' during brain perfusion studies with SPET. This approach can yield information about specific brain mechanisms associated with such tasks, and may make comparison with healthy volunteers easier.

INTRODUCTION

The late positive event related potential (ERP), which is generated in response to an auditory 'oddball' discrimination task after 300 ms post-stimulus (P300), is abnormally reduced in amplitude and prolonged in latency in schizophrenic patients when compared with controls (Pfefferbaum *et al*. 1984; Blackwood *et al*. 1987). Evidence derived from a variety of methods suggests that areas within the superior temporal and inferior parietal regions are responsible for P300 generation. These methods include depth-electrode recordings (Halgren *et al*. 1980; Smith *et al*. 1986, 1990; Meador *et al*. 1987; Stapleton & Halgren, 1987; Richer *et al*. 1989), topographic analysis (Lovrich *et al*. 1988) and studies of patients with discrete brain lesions (Knight *et al*. 1988, 1989). More recently, a positron emission tomography (PET) study during P300 activation has shown activation in temporal and cingulate areas during an auditory discrimination task in healthy volunteers (Ohyama *et al*. 1993). In a further experiment (Ebmeier, 1995), split-dose single photon emission tomography (SPET or SPECT) scans were obtained from healthy elderly volunteers while they performed different auditory 'oddball' discrimination tasks. During a two-tone task there was a bilateral posterior temporal and medial frontal

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activation, a left pericentral increase and posterior cingulate suppression compared with a resting control group.

This study measures brain perfusion in a group of schizophrenic patients who are performing a two-tone auditory discrimination task and correlates ERP-latencies and amplitudes with perfusion during the task. In addition, a within-subject comparison of SPET scans between the two-tone 'activation' state and a 'resting' state is made, using the split-dose technique for SPET described earlier (Ebmeier *et al*. 1991). The rationale for evaluating such a task was three-fold: (1) performing a task is likely to homogenize patient brain maps and make comparisons with controls more valid (Weinberger, 1988); (2) using a simple task that can be performed by all patients helps to avoid task-performance issues that could confound group differences (cf. Ebmeier *et al*. 1995; Gur & Gur, 1995); and (3) the P300 abnormalities observable in schizophrenic patients are readily quantifiable in terms of ERP amplitudes and latencies.

We hypothesized that (1) activation during the 'oddball task' would be associated with blood flow changes in the temporo-parietal areas which are implicated in P300 generation. Furthermore (2), we predicted that these blood flow changes were correlated with P300 latency and amplitude. As it is likely that cingulate areas are involved in modulating the P300 response we also (3) expected cingulate blood flow changes during activation which were (4) correlated with the degree of P300 abnormality.

METHOD

Patients

Twenty patients (12 male) participated in the study. Eighteen were in-patients, two were out-patients at the Royal Edinburgh Hospital. Exclusion criteria were: (1) significant head injury; (2) any neurological disorder; (3) current abuse of alcohol or drugs; and (4) other significant medical illnesses likely to affect the nervous system. Subjects were interviewed according to the Schedule for Affective Disorders and Schizophrenia-lifetime version (SADS-L). All met the DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia, based on the interview, case-notes and third party information. Seventeen of the 20 subjects were receiving neuroleptic medication, the other three were neuroleptic-free for at least 6 months. Eighteen of the 20 subjects were unequivocally right-handed, as assessed by the Handedness Scale (Annett, 1970). Sociodemographic and clinical characteristics of the patients are summarized in Table 1. All subjects gave informed and written consent for clinical evaluation, ERP recording and the imaging procedure, according to protocols approved by the local ethics committee and the Administration of Radioactive Substances Advisory Committee (ARSAC) at the UK Department of Health (RPC 470–3 (5)).

Table 1. *Demographic and clinical data*

	Mean $N = 20$	S.D.
Demographic data		
Age (years)	34·8	11·8
Education (years)	12·4	2·8
WAIS-R IQ	102·7	19·0
NART IQ	103·1	13·1
Clinical data		
Illness onset age (years)	24·9	5·9
Brief Psychiatric Rating Scale	19·6	9·1
BPRS disorganization	1·4	1·3
BPRS psychomotor poverty	5·1	2·4
BPRS reality distortion	3·3	3·2
Hamilton Depression Scale	8·0	5·2
Bech–Rafaelsen Mania Scale	1·5	2·0
Chlorpromazine equivalent (mg/day)	409·3	311·7

WAIS-R, Wechsler Adult Intelligence Scale-Revised; NART, National Adult Reading Test; BPRS, Brief Psychiatric Rating Scale.

Clinical and neuropsychological assessment

Clinical symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), Hamilton Depression Rating Scale (Hamilton, 1960) and Bech–Rafaelsen Scale for manic symptoms (Bech *et al*. 1979). The BPRS was further subdivided into poverty syndrome, disorganization and reality distortion according to Liddle *et al*. (1992). Neuroleptic dosages (oral and depot) were converted to chlorpromazine equivalents (Bazire, 1993).

Pre-morbid intelligence was estimated using the National Adult Reading Test (NART), which has been validated in acutely ill schizophrenic populations (O'Carroll *et al*. 1992).

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Current intellectual ability was estimated from the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981) subsets of block design and vocabulary. Details of further neuropsychological assessment have been reported elsewhere (Shajahan *et al*. 1996).

Event-related potentials

Event-related potentials (ERPs) were recorded on the day before the SPET scan and within 5 days of neuropsychology testing, all investigations were done at the same time of day. Unipolar silver/silver chloride electrodes were placed at frontal (Fz), central (Cz), parietal (Pz), and linked ear electrodes, according to the 10–20 system (Jasper, 1958). The bipolar electrooculogram (EOG) was recorded supra-orbitally and at the lateral canthus of the left eye, the amplifier reference was placed on the forehead. All impedances were below 5 kΩ. The electroencephalogram (EEG) was amplified by 10000 with a bandwidth of 0·16 to 30 Hz (−3 dB) by a Digimeter D-160 amplifier system. The data were then sampled via an analogue to digital converter with 12-bit resolution at 250 Hz per channel. The 244 ms of pre-stimulus baseline were followed by the stimulus and 752 ms of post-stimulus data. All data exceeding ±45 μV peak size caused automatic rejection of the whole data sweep. Prior to processing, data were smoothed with a bi-directional digital filter (15 Hz (−3 dB), 1 pole, low-pass Butterworth). Tones of 40 ms duration were generated at 1000 Hz (85%) and 1500 Hz (15%). Auditory stimuli were delivered binaurally through headphones at an intensity of 75 dB (SPL) and a stimulus interval of 1·1 s. Subjects were instructed to count silently the infrequent high-pitched notes. During the procedure a total of 40 rare tones were presented. The P300 latency was measured by the least-mean-squares (LMS) method (Glabus *et al*. 1994) and amplitude (μV) was defined as the highest point in a pre-defined window (280–550 ms). Latencies and amplitudes could be determined in 17 out of 20 patients, the other three could not be analysed due to recording artefacts, or lack of consensus between three raters in determining the window for the LMS fit.

In order to assess the validity of using ERP data for correlations with brain activity measures acquired one day later, albeit under the same testing paradigm, ERPs were recorded in 10 randomly selected patients 1 day before and 1 day after the scan. The time of day of the ERP recording was kept constant. Recorded at Pz the N1-amplitudes were −2·1 and −2·4 μV (effect size, d = 0·61), with a correlation of $r = 0{\cdot}73$. N1-latencies were 110 and 101 ms (d = 0·91), with a correlation of $r = 0{\cdot}49$. P300-amplitudes were 9·1 and 9·7 μV (d = 0·40), with a correlation of $r = 0{\cdot}73$, P300-latencies were 370 and 358 ms (d = 0·77), with $r = 0{\cdot}82$. Only N1-latencies were not reliable enough ($r < 0{\cdot}7$) to proceed with the correlational analyses.

Single photon emission tomography

All subjects were imaged with a high resolution single slice multi-detector head scanner (Neuro 900, Strichman Medical Equipment Inc., Boston, USA). The scanner consists of 12 detectors with a maximum in-slice and z-axis resolution of 7·5 mm. Each subject received 2 × 250 MBq of ^{99m}Tc-Exametazime (HM-PAO), resulting in a total effective dose equivalent of between 5 and 6 mSv (Picket *et al*. 1995). During the activation condition, subjects were asked to lie comfortably on the imaging table with their eyes closed and covered. A tape recording specifically prepared to reproduce the 'oddball' paradigm of the ERP procedure with the same sound intensity and stimulus parameters was then placed, via a set of calibrated headphones, for a total of 210 s. Subjects were asked to count the 1500 Hz target tones silently and report the number afterwards. All counts were accurate within ±10%. Thirty seconds into the recording, the tracer was injected (injection time 30 s). The subjects were asked to lie still for a further 60 s after the stimuli had ceased. The resting baseline condition was identical to the activation condition with the exception that no stimuli were played through the headphones. Five minutes after each injection, state anxiety was measured using the Alderly Park State Anxiety Questionnaire (APSAQ) (Walker, 1990). There were no significant differences between APSAQ scores during baseline and activation ($t = 0{\cdot}65$, df = 17, $P = 0{\cdot}52$). Following this, the subject's head was positioned into a head rest, aided by crossed positioning lights. The head was fixed with pressure pads on the

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Table 2. *Peak effects* (P < 0·001) *of activation and correlation with P*300 *amplitude*

	Increased perfusion					Decreased perfusion				
Effect	Region	*Z*	*x*	y	z	Region	*Z*	*x*	y	z
Task minus rest	L Superior Temporal Gyrus (BA 22, 42)	3·46	−58	−34	8					
	R Caudate	3·45	10	−10	20					
P3-amplitude						L Caudate	3·17	−20	0	24
							3·01	−28	−38	16
						L Lingual Gyrus (BA 18)	3·15	−26	−72	4
						R Caudate	3·78	28	−6	24
							3·14	20	−22	20
							2·97	28	−36	16

BA, Brodmann's area; L, left; R, right; *Z* = peak *z* value for effect examined; *xyz* = coordinates in Talairach atlas.

zygomatic arches. Slices were acquired parallel to the orbito-meatal plane starting at a level approximately 2 cm above the orbito-meatal (OM) line and at 1 cm intervals above this level.

Image analysis

Data were processed using software supplied by Strichmann Medical Equipment (SME) on a variety of Apple Macintosh computers, and using Analyze (CNS Software) and custom written software developed in the MATLAB (The Mathworks, Inc.) on Sun SPARC workstations. Statistical parametric maps were derived using the SPM software (version SPM'95, supplied by K. J. Friston and colleagues at the Wellcome Department of Cognitive Neurology, Institute of Neurology, Functional Imaging Laboratory, 12 Queen Square, London WC1N 3BG).

The data processing procedures typically followed the pattern shown below.

1 Manual yaw, roll and pitch correction of images was followed by an automated maximum ρ, cross-correlation algorithm co-registration of image-pairs from the same subject in the SME scanning software (Neuro 900 version 2.92). Images were then edited to ensure they contained the same number of slices over equivalent brain volumes.

2 Images were exported as binary files and converted to Analyze format.

3 The first scan was decay-corrected and subtracted from the second scan, to produce an activity map reflecting the brain state at the time of the second injection.

4 The scan pairs were spatially normalized using a 12-point linear affine transformation into Talairach space. The transformation elements were derived from the average of both scans from each subject and applied to each identically (Friston *et al.* 1995). The images were then smoothed with an isotropic (12 mm FWHM) Gaussian filter in order to reduce the error variance associated with individual variability in gyral anatomy and to improve the signal to noise ratio.

5 Data were analysed using an ANCOVA blocked design (one block per subject) with two conditions (rest/task), psycho-physiological co-variates (N1 and P300 amplitudes and latencies), and two confounder variables (global tracer uptake and age).

Statistics

Effects are reported, if peak *P* values are smaller than or equal to 0·001 without controlling for multiple comparisons. This is an empirical cut-off point which has been considered to provide a good protection against false positive results (Frith *et al.* 1991).

RESULTS

Table 2 and Figs. 1 and 2 summarize the results of the statistical parametric mapping analysis. There were peak increases ($P < 0{\cdot}001$) in tracer uptake in left superior temporal gyrus and right caudate during the 'oddball task'. A higher P300-amplitude was associated with decreased perfusion in both caudates and right lingual gyrus. There were no significant reductions in perfusion from rest to activation, neither were there any significant correlations between other ERP measures and perfusion during the task.

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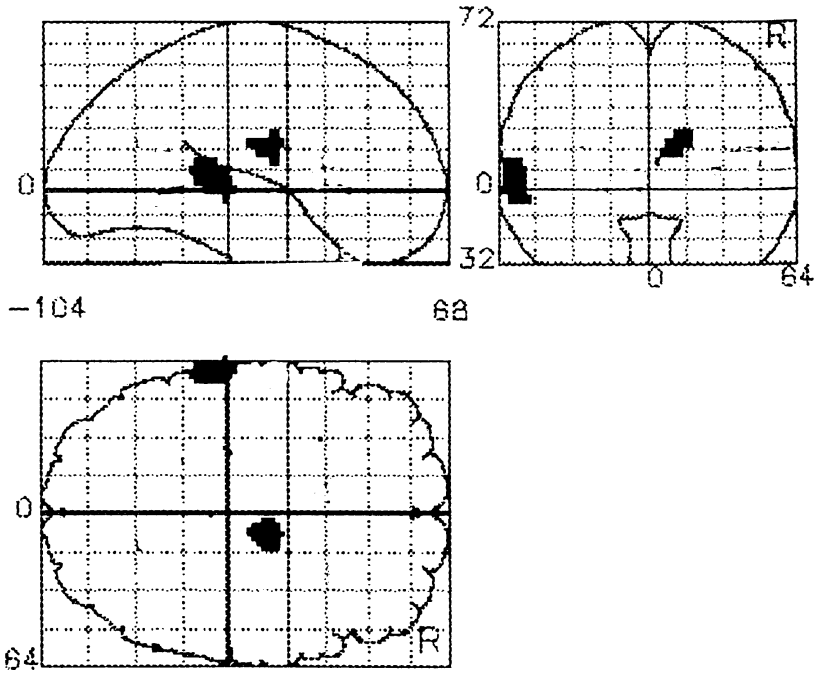


FIG. 1. Activation with peaks ($P < 0{\cdot}001$) (the surrounding volume with $P < 0{\cdot}01$ is also shown).

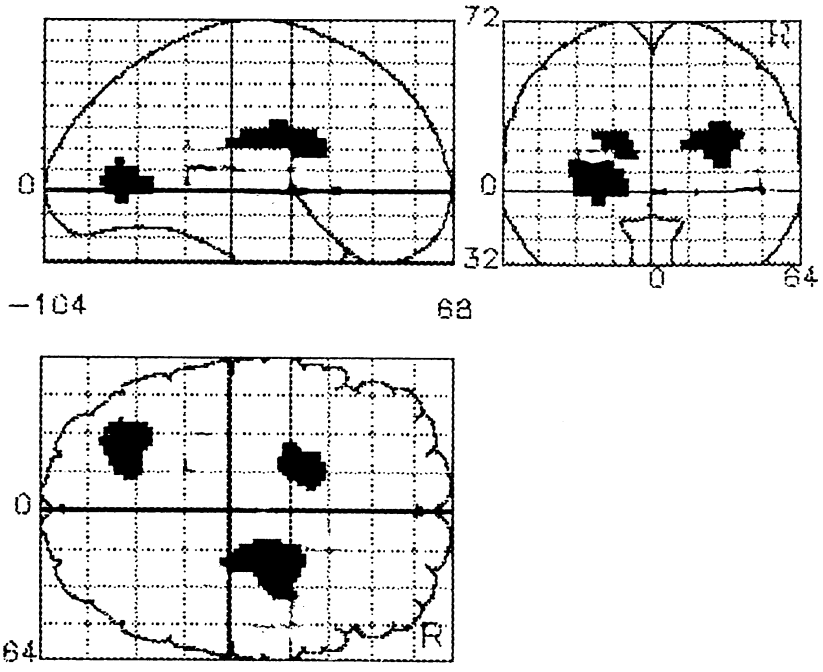


FIG. 2. Negative correlations with P300-amplitude with peaks ($P < 0{\cdot}001$) (the surrounding volume with $P < 0{\cdot}01$ is also shown).

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DISCUSSION

In summary, patients activated the left superior temporal gyrus and right caudate nucleus during the task. There was a negative correlation between P300-amplitude and perfusion during the activation procedure in both caudate nuclei and in the left lingual gyrus. Compared with healthy volunteers examined in earlier studies, our patients showed no frontal activation.

We were, thus, able to confirm our first hypothesis that activation during the 'oddball task' would be associated with perfusion changes in temporo-parietal areas. An excess in left (temporal) perfusion has been described in schizophrenic patients already at rest, and particularly in the presence of hallucinations and delusions (Kawasaki *et al.* 1992; Liddle *et al.* 1992; Suzuki *et al.* 1993). It is possible that this effect of the illness was enhanced by the task. The localization in the posterior aspects of the temporal lobe is consistent with our earlier study (Ebmeier *et al.* 1995) and P300-studies in patients with temporal lobe epilepsy after (anterior) lobectomy, who can still produce intact P300s (Stapleton *et al.* 1987; Johnson, 1989). In a more recent O^{15}-PET study, comparing a two-tone P300 condition against a non-targets only baseline condition, Reinsel and co-workers described temporal activation at almost exactly the same location as our study ({−60, −34, 12}, cf. Table 2), suggesting that left unilateral activation is associated with 'oddball'-tasks in general, also in healthy volunteers (Reinsel *et al.* 1995). An alternative explanation is that studies using a silent counting task (Reinsel 1995, this study) show only left-sided temporal activation, while reaction time (button pressing) tasks (Ohyama *et al.* 1993; Ebmeier, 1995) are associated with bilateral temporal activation.

The absence of left pericentral activation in comparison with the Ebmeier *et al.* (1995) study can be explained by the difference in tasks, silent counting in this, button press with the right hand in the earlier study. The lack of medial frontal activation (hypothesis 3) is more difficult to explain. The counting task might lack the frontal activation associated with a motor task observed in both the Ohyama *et al.* (1993) and Ebmeier *et al.* (1995) studies. However, the counting task in the Reinsel *et al.* study (1995) was associated with frontal activation. An absence of frontal activation has already been described in schizophrenic patients by a number of authors during neuro-psychological tasks (reviewed in Ebmeier, 1995). It is, therefore, possible that the same 'hypofrontality' can be observed in psycho-physiological tasks. To test this hypothesis, a parallel study with age matched healthy volunteers may be necessary. The complexities of scanning during neuro-psychological activations with impaired task performance in patients (Ebmeier, 1995) could be circumvented by simpler psycho-physiological tasks which can be performed by all patients.

There were no positive correlations between P300 amplitude and perfusion (hypotheses 2 and 4), that would have been interpretable in terms of neurone numbers recruited during the task. This may be due to the lack of a more widespread activation (cf. Ebmeier *et al.* 1995), maybe reflecting the abnormal brain response to the task in schizophrenic patients. Instead, there were negative correlations, particularly in the caudate nuclei. The connection of basal ganglia with frontal structures and the involvement of basal ganglia in schizophrenia – in terms of perfusion increases (Early *et al.* 1987) – provide a possible explanation of this finding.

The present study is one of the first SPET studies in schizophrenia to exploit a repeat measures design to localize brain changes associated with an activation task and using a pixel-by-pixel method of image analysis. Statistical Parametric Mapping (SPM), originally designed for multi-slice high-resolution PET, is here applied to single slice high-resolution SPET. This presupposes a tracer that does not change in distribution over the time of the scan, a condition likely to be fulfilled by ^{99m}Tc-HM-PAO. Another condition is the immobility of the patient's head throughout the whole scan. We have previously shown that our head fixation and repositioning procedure gives repeat measures of high reliability (Ebmeier *et al.* 1991). We have also demonstrated that subtracting the activity remaining of the first injection from the second scan allows an estimation of physiological activation effect sizes consistent with PET results from similar experiments (Ebmeier *et al.* 1992).

A number of further methodological issues need discussing. The time window for the incorporation of the perfusion tracer (1–2 min

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of first pass through the brain) is much wider than the time window used for the recording of target or non-target ERPs. This means that during tracer uptake up to 16 targets and 90 non-targets would have occurred, so that their relative contribution to the final perfusion map is not known. We chose the contrast with rest rather than, for example, a series of non-targets, because our purpose was to establish the largest, most robust effect of the overall 'oddball task' on perfusion. Interestingly, our results did not differ substantially from the Reinsel *et al*. study (1995), which used non-targets alone as a baseline.

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