

A fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics



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Abstract

A key feature of schizophrenia is the inability to screen out irrelevant sensory input. Prepulse inhibition (PPI) of the startle response, a cross-species measure of sensorimotor gating, provides a valuable opportunity to study this feature. PPI is reliably impaired in schizophrenia. Animal models of disrupted PPI have proved valuable for the evaluation of antipsychotic substances. The cortico-striato-pallido-thalamic circuitry is primarily responsible for modulation of PPI in animals. We examined PPI and its brain correlates, using functional magnetic resonance imaging (fMRI), in men with schizophrenia treated with typical or atypical antipsychotics. Thirty men with schizophrenia on stable doses of typical antipsychotics ($n=10$), risperidone ($n=10$) or olanzapine ($n=10$; 9 with usable fMRI data) and 12 healthy men underwent psychophysiological testing and fMRI during a tactile PPI paradigm. The results showed reduced PPI of the eye-blink startle response in patients compared with healthy controls. Within the patient group, those on typical antipsychotics showed significantly impaired PPI but risperidone- or olanzapine-treated patients showed a milder (non-significant) deficit. Increased activity in the striatum, thalamus, insula, hippocampal, temporal, inferior frontal and inferior parietal regions occurred in association with PPI in controls. Patients treated with risperidone or olanzapine, but not with typical antipsychotics, showed significant activation in PPI-relevant regions. Our findings provide preliminary evidence that atypical antipsychotics positively influence PPI and partially restore associated brain functions in schizophrenia. Imaging data buttress the validity of PPI as a useful animal model of schizophrenia.

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Introduction

The simple startle reflexive response shows several forms of plasticity, including prepulse inhibition (PPI). PPI refers to a reliable reduction in the amplitude of the startle response to a strong sensory stimulus, the pulse, if this is preceded shortly (30–500 ms) by a weak stimulus, the prepulse (Graham, 1975). PPI offers a simple operational measure of sensorimotor gating, serving to prevent the interruption of ongoing

perceptual and early sensory analysis. Animal studies have shown that PPI is modulated by the cortico-striatal-pallido-thalamic (CSPT) circuitry involving the prefrontal cortex, thalamus, hippocampus, amygdala, nucleus accumbens, striatum, ventral pallidum, globus pallidus, and subpallidal efferents to the pedunclopontine nucleus (for reviews see Swerdlow and Geyer, 1998; Swerdlow et al., 2001). Recent functional (Hazlett et al., 1998, 2001; Kumari et al., 2003) and structural (Kumari et al., 2005b) neuroimaging studies confirm that these regions are also involved in PPI in healthy human subjects.

Pharmacological and surgical challenges to substrates of the CSPT circuitry reliably produce change in PPI in experimental animals which is consistent

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with the hypothesis that the impaired gating seen in schizophrenia may arise from abnormalities in the neural interactions between limbic structures and basal ganglia (for reviews see Swerdlow and Geyer, 1998; Swerdlow et al., 2001).

PPI is considered a well-validated animal model for evaluating existing and potential new treatments for schizophrenia for several reasons (Geyer et al., 2001; Geyer and Ellenbroek, 2003; Swerdlow and Geyer, 1998). First, there is excellent evidence that PPI is disrupted in schizophrenia (Braff et al., 1978, 2001; Duncan et al., 2003a,b; Kumari et al., 2005b; Leumann et al., 2002; Ludewig et al., 2003; Mackeprang et al., 2002; Meincke et al., 2004; Oranje et al., 2002). Second, PPI shows similar sensitivity to stimulus characteristics in rats and human beings (Swerdlow et al., 1994). Third, PPI in rats is disrupted and potentiated by drugs that have psychotic and antipsychotic properties, respectively, in humans (Swerdlow and Geyer, 1998; Geyer et al., 2001; Geyer and Ellenbroek, 2003). Environmental manipulations with relevance to schizophrenia, such as isolation rearing and viral infection, also disrupt PPI and such disruptions too can be reversed by antipsychotic drugs (Powell and Geyer, 2002). Furthermore, some PPI models are able to distinguish between antipsychotic drugs with typical and atypical properties. Dopamine (DA) agonists, serotonin (5-HT) agonists and *N*-methyl-D-aspartate (NMDA) antagonists disrupt PPI (Geyer et al., 2001; Swerdlow et al., 1992; Swerdlow and Geyer, 1998). DA agonist-induced disruptions can be reversed by both typical and atypical antipsychotics (Geyer et al., 2001; Swerdlow et al., 1992; Swerdlow and Geyer, 1998). However, atypical antipsychotics, such as clozapine, show superiority to typical antipsychotics in restoring PPI deficits induced by other pharmacological manipulations, for example, the disruption of PPI by phencyclidine (Geyer et al., 2001; Geyer and Ellenbroek, 2003; Swerdlow and Geyer, 1998). Atypical antipsychotics also show superiority in reversing the disruption of PPI in some neurodevelopmental models (Le Pen and Moreau, 2002). These findings suggest that atypical antipsychotics should be more effective in restoring PPI deficits in schizophrenia patients, especially in those suffering from dysfunctions across several neurotransmitter systems (see review by Kumari and Ettinger, 2005).

In line with preclinical evidence, one study (Weike et al., 2000) reported improved PPI with effective, typical or atypical, antipsychotic medication in schizophrenia patients. Studies from three different research groups have reported 'normal range' PPI in patients on atypical antipsychotics but significantly

reduced PPI in those on typical antipsychotics (Kumari et al., 1999, 2000, 2002; Leumann et al., 2002; Oranje et al., 2002). A longitudinal study (Meincke et al., 2004) reported increased PPI in schizophrenia patients with improvement in their symptoms after medication, suggesting state-related changes in PPI. Another recent longitudinal study (Quednow et al., 2006) observed a significant PPI deficit in schizophrenia patients at baseline but this deficit disappeared after 4 wk treatment with amisulpride or olanzapine. However, there are other studies which failed to observe an effect of antipsychotic medication on PPI (Duncan et al., 2003a,b; Mackeprang et al., 2002; Parwani et al., 2000; Perry et al. 2002). To what extent inconsistent findings on medication influences in PPI in schizophrenia reflect procedural differences, sample characteristics, the effects of specific compounds under investigation, or treatment responsiveness remains to be clarified (for review see Kumari and Ettinger, 2005). This area should be considered an important line of enquiry given the use of PPI as a model to screen new compounds for their antipsychotic actions and atypicality.

In the present study, we investigated tactile PPI and its brain correlates, using functional magnetic resonance imaging (fMRI) in homogenous groups (as far as possible) of men with schizophrenia who were stable on typical antipsychotics or one of the two commonly used atypical antipsychotics, namely risperidone and olanzapine. Only two published studies (Hazlett et al., 1998; Kumari et al., 2003) have so far focused on the neural mechanisms that might be associated with reduced PPI in schizophrenia patients. Of these, one study (Hazlett et al., 1998) used positron emission tomography and did not examine limbic regions while the other study (Kumari et al., 2003) examined only a small number of patients ($n=6$) all of whom were treated with typical antipsychotics. No imaging data, to our knowledge, are available on neural correlates of PPI in patients treated with atypical antipsychotics.

Our primary aim was to test the hypotheses that: (i) abnormal patterns of activation will be demonstrated in patients in the striatal, thalamic, temporal and parietal regions that are found to subservise PPI in healthy people (Hazlett et al., 2001; Kumari et al., 2003), and (ii) within the patient groups, the largest PPI deficit and associated functional brain abnormalities would be found in patients on typical antipsychotics, with less severe (or no) deficits in those on risperidone or olanzapine. Our secondary aim was to confirm previously reported associations between reduced PPI and increased distractibility (Karper et al., 1996;

Table 1. Demographics and clinical characteristics

	Control group (<i>n</i> = 12)	Typical antipsychotics group (<i>n</i> = 10)	Risperidone group (<i>n</i> = 10)	Olanzapine group (<i>n</i> = 10)
Age (yr)	36.25 (11.12)	39.00 (8.33)	33.20 (11.51)	40.20 (11.96)
Predicted IQ (NART) ^a	116.75 (10.67)	101.70 (13.84)	94.00 (12.64)	103.70 (11.36)
Years of education	15.37 (3.09)	12.60 (3.80)	11.90 (1.45)	13.70 (3.86)
Positive symptoms ^b		13.70 (3.81)	12.60 (4.45)	12.80 (3.99)
Negative symptoms ^b		13.69 (5.13)	12.10 (4.82)	15.65 (5.70)
General psychopathology ^b		33.60 (12.78)	26.90 (5.74)	33.10 (14.94)
Total PANSS scores ^b		61.00 (18.79)	51.60 (10.92)	59.60 (22.46)
Barnes Akathisia score		0.20 (0.63)	0.20 (0.63)	0.30 (0.95)
Age at illness onset (yr) (appearance of psychotic symptoms)		21.80 (5.20)	24.70 (8.86)	24.70 (8.31)
Smokers (<i>n</i>)	7/12	7/12	6/10	7/10

^a NART, National Adult Reading Test (Nelson and Willison, 1991).

^b Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

n = 24) and reduced executive functioning (Butler et al., 1991; *n* = 15) in patients with schizophrenia.

Method and materials

Participants

The study involved 30 male patients with schizophrenia. Of these 30 patients, 10 were on a range of typical antipsychotics (5 on haloperidol, 2 on chlorpromazine, and 3 on flupenthixol; mean daily dose in chlorpromazine equivalents 430.27 mg/d, *s.d.* = 368.96), 10 on risperidone (mean daily dose 3.9 mg, range 2–8 mg/d), and 10 on olanzapine (mean daily dose 18.0 mg, range 10–50 mg/d). All included patients were diagnosed as having schizophrenia by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). All patients had been on the same antipsychotic for 4 months or longer and were deemed treatment responsive by their treating clinicians. In addition, two patients (one on risperidone and one on typical antipsychotics) were taking procyclidine (10 mg/d). They had no history of neurological disease or alcohol or other substance abuse in the preceding 6 months and were free from illicit drugs at the time of this study (confirmed with urine analysis). Table 1 presents demographic and clinical characteristics of patients classified by their medication type.

Twelve healthy men, who were screened using a semi-structured interview (SCID; First et al., 1996) and found not to have a history of mental illness, anorexia, drug and alcohol abuse (confirmed with urine screen),

regular medical prescription, or presence of psychosis in their first-degree relatives, were examined for comparison purposes. All included participants (patients and controls) were strongly right-handed as determined using the Edinburgh Handedness Inventory, shortened version (Oldfield, 1971).

The study procedures were approved by the ethics committee (research) of the Institute of Psychiatry and Maudsley Hospital, London. All participants provided written informed consent.

Clinical assessments

Symptoms were rated within 4 d of scanning using the Positive and Negative Syndrome scale (PANSS; Kay et al., 1987) by a trained psychiatrist. Side-effects were also recorded within 4 d of scanning using the Barnes Akathisia Scale (Barnes, 1989).

PPI experiment: paradigm and procedure

The PPI paradigm involved the use of tactile stimuli as both the pulse (a 40-ms presentation of 30 psi air-puff) and the prepulse (a 20-ms presentation of 6 psi air-puff). There were four conditions in total [30-ms stimulus onset asynchrony (SOA) PPI, 120-ms SOA PPI, pulse-alone, prepulse-alone] each presented to participants five times in 30-s blocks in pseudorandom order, controlling for any order effect, all starting with a 15-s resting baseline. Six stimuli were presented (inter-stimulus interval of 3–6 s) within each 30-s block. The pulse-alone condition involved presentations of the pulse stimulus and the prepulse condition

involved presentation of the prepulse stimulus. In the 30-ms and 120-ms SOA PPI conditions, the pulse stimulus was presented preceded by the prepulse stimulus with SOA of 30 ms or 120 ms. The experiment lasted about 15 min.

All stimulus presentation during the scanning and psychophysiological testing was controlled by a commercially available Human Startle Response Monitoring System (SR-Lab, San Diego Instruments, San Diego, CA, USA). The air-puff delivery system consisted of two cylinders of compressed clean air (one for the pulse, and the other for the prepulse), each with a solenoid-controlled valve and a 10-m long plastic tube (diameter 6 mm) (as described by Kumari et al., 2003). The tubes were taped together, applied to the subject's neck in the midline just above the sternum, and secured with tape.

All potential participants underwent psychophysiological testing for PPI of the eye-blink reflex response on the morning of the scheduled scan or 1 d in advance. At the time of this study, it was not possible to safely use electrodes to measure PPI electromyographically during the scanning itself. However, PPI has been shown to have high stability in both normal (Abel et al., 1998; Cadenhead et al., 1999; Flaten, 2002; Schwarzkopf et al., 1993) and clinically stable schizophrenia subjects (Ludewig et al., 2002) and thus was expected to occur in participants during the scanning in proportion to what they showed in the psychophysiology laboratory. Only those participants were included in the fMRI experiment who responded (produced a clearly visible blink) to the first two tactile stimuli (one control and two patients were excluded on this account) and did not show a startle response to the prepulse stimuli (one control and one patient were discarded). Those excluded after the psychophysiological screening were in addition to the sample reported here.

Cigarette smokers were allowed to smoke as usual on days of fMRI and psychophysiological testing to avoid a state of smoking/nicotine withdrawal which would affect PPI (Kumari and Gray, 1999) but care was also taken not to start psychophysiological recording/scanning of them within 30 min of smoking a cigarette to avoid the possibility of a transient increase in PPI due to nicotine intake (Kumari et al., 2001).

Psychophysiological data collection

The eye-blink component of the startle response was measured by recording the electromyographic (EMG) activity of the right orbicularis oculi muscle via two (contact area < 4 mm) Ag/AgCl electrodes filled with

Dracard electrode gel. After preparing the skin surface with Sterets sterile swabs, one electrode was positioned ~1 cm lateral to, and 0.5 cm below, the lateral canthus of the subject's right eye, while the second electrode was placed 1.5 cm below and slightly medial to the first electrode, such that both electrodes were equidistant from the centre of the eye. In addition a ground (reference) electrode was placed behind the right ear over the mastoid. The startle system recorded EMG activity for 250 ms (sample interval 1 ms) from the onset of the startle stimulus. The amplification gain control for EMG signal was kept constant for all subjects. Recorded EMG activity was band-pass filtered, as recommended by SR-Lab. Analogue band-pass filtering occurred before digitizing. The high-pass and low-pass cut-off frequencies were set at 100 Hz and 1 kHz respectively. A 50-Hz notch filter was used to eliminate the 50-Hz interference. The data were scored offline by the analytical programme of this system for response amplitude (in arbitrary analogue-to-digit units), and latencies to response peak (in ms). The scoring programme contained a rolling average routine which smoothed the rectified EMG response. The latency to response peak was determined as the point of maximal amplitude that occurred within 120 ms from the startle stimulus. PPI was computed as $[(a - b)/a] \times 100$, where a = pulse-alone startle amplitude and b = prepulse + pulse amplitude.

Image acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee, WI, USA) at the Maudsley Hospital, London. Daily quality assurance was carried out to ensure high signal-to-ghost ratio, high signal-to-noise ratio and excellent temporal stability using an automated quality control procedure (Simmons et al., 1999). A quadrature birdcage head coil was used for RF transmission and reception. In each of 36 near-axial non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 300 T2*-weighted MR images depicting blood-oxygen-level-dependent (BOLD) contrast (Ogawa et al., 1990) were acquired over the experiment with echo time (TE) = 40 ms, repetition time (TR) = 2 s, in-plane resolution = 3.0 mm, slice thickness = 3.0 mm, interslice gap = 0.3 mm. In the same session, a high-resolution 3D inversion recovery prepared spoiled GRASS volume dataset was acquired with TE = 5.3 ms, TI = 300 ms, TR = 12.2 ms, in-plane resolution = 0.94 mm, slice thickness = 1.5 mm. Participants were not required to make any voluntary responses during the scanning.

Neuropsychological assessments

The neuropsychological tests of attention (Continuous Performance Task, identical pairs version; CPT-IP, Cornblatt et al., 1988), executive functioning [Wisconsin Card Sorting Test (WCST), computerized version, Heaton, 1993] and also of mental flexibility (Trail Making Test, forms A and B, Reitan and Wolfson, 1985) were administered by a trained psychologist within a week of scanning. Predicted verbal IQ of all participants was assessed using the National Adult Reading Test (NART revised; Nelson and Willison, 1991) for sample characterization purposes. All participants were administered tests in the same order.

Data analysis

All demographic, clinical, cognitive and psychophysiological data were analysed using SPSS version 12.00 (SPSS Inc., Chicago, IL, USA). The α -level for significance (two-tailed) was set at $p < 0.05$ unless indicated otherwise.

Clinical measures

Symptoms and side-effects in the three patient groups were analysed with one-way analysis of variance (ANOVA).

Psychophysiological measures: startle amplitude, habituation and PPI

To examine the difference between the patient and control groups in the amplitude and habituation of the startle response over the experiment, the data from the pulse-alone condition were subjected to a 2 (diagnosis: patients, controls) \times 5 (block: five 30-s blocks each consisting of six trials) ANOVA, with diagnosis as a between-subjects and block as a within-subjects factor. A further 4 (group: controls, patients on typical antipsychotics, patients on risperidone, and patients on olanzapine) \times 5 (block) ANOVA was conducted to compare the groups against each other on response amplitude and habituation.

To examine the difference in PPI between the patient and control groups, PPI (%) scores were subjected to a 2 (diagnosis) \times 2 (trial type: 30-ms SOA PPI; 120-ms SOA PPI) ANOVA, with diagnosis as a between-subjects and trial type as a within-subjects factor. As for the amplitude and habituation, a further 4 (group) \times 2 (trial type) ANOVA was conducted with relevant post-hoc comparisons to compare the patient groups (classified by the medication type) against the control group. Although we did not have sufficient

power to detect significant differences between the patient groups given the small effect for superiority of atypical antipsychotics over the typical ones (where found) in previous reported studies of schizophrenia patients (for review see Kumari and Ettinger, 2005), we explored the differences between the patient subgroups in post-hoc comparisons.

Latencies to response peak were analysed with a 2 (diagnosis) \times 3 (experimental condition: pulse-alone, 30-ms SOA PPI, 120-ms SOA PPI), followed by a 4 (group) \times 3 (experimental condition: as for the previous ANOVA) ANOVA.

fMRI of PPI

Image pre-processing

For each subject, the 300 volume functional time series were motion corrected (Friston et al., 1996), transformed into stereotactic space, spatially smoothed with a 6-mm FWHM Gaussian filter and band-pass filtered using statistical parametric mapping software (SPM99; <http://www.fil.ion.ucl.ac.uk/spm>). Imaging data (incomplete due to problems during acquisition) for one patient on olanzapine were found to be unusable, thus reducing the sample size for this group (for fMRI part only) to nine patients.

Models and inferences

Data were analysed using a random-effect procedure (Friston et al., 1999). The first stage identified subject-specific activations in all participants with a factorial model consisting of four conditions (pulse-alone, pre-pulse-alone, 30-ms SOA PPI, 120-ms SOA PPI) and rest as an implicit baseline. The boxcar for each 30-s epoch was convolved with the haemodynamic response function. Generic task-related activations in each group were identified (corrected for multiple comparisons at the cluster level, $p < 0.005$, unless indicated otherwise) for the 120-ms SOA PPI > pulse-alone and 30-ms SOA PPI > pulse-alone contrasts using one-sample t tests. The 30-ms SOA PPI > pulse-alone contrast failed to elicit reliable and sufficiently strong activation even in the control group (see Results section) and thus was not taken up at the second stage of analysis.

The second stage of analysis compared patients, as a group, with controls using between-subject t tests on the 120-ms SOA PPI > pulse-alone contrast. We then evaluated the relationships between BOLD response in regions found to differentiate patients from controls and PPI across the entire sample. Next, we performed an ANOVA within SPM for the 120-ms

Table 2. Mean (standard error of the mean) response amplitudes (in A/D units) over the five blocks of six pulse-alone trials each in controls and patients with schizophrenia

Blocks	Controls (<i>n</i> = 12)	All patients (<i>n</i> = 30)	Typical antipsychotics group (<i>n</i> = 10)	Risperidone group (<i>n</i> = 10)	Olanzapine group (<i>n</i> = 10)
1	363.06 (49.47)	457.78 (75.07)	304.20 (86.18)	588.29 (79.45)	480.86 (101.34)
2	220.75 (33.17)	306.14 (51.83)	214.11 (48.71)	344.67 (91.66)	359.64 (117.34)
3	161.42 (26.92)	258.86 (41.35)	207.07 (43.72)	291.42 (81.25)	278.10 (86.93)
4	160.18 (23.86)	267.24 (42.16)	220.06 (51.71)	252.79 (63.51)	328.89 (98.89)
5	151.39 (23.07)	238.67 (47.38)	223.44 (75.13)	238.36 (75.65)	254.19 (101.40)

SOA PPI > pulse-alone contrast with the four groups as a between-subjects factor to identify regions ($p < 0.05$, corrected for multiple comparisons at the cluster level), differentiating one or more of the patient groups from the control group. We found no significant clusters reaching these criteria. We then re-evaluated the results using a more lenient criteria ($p < 0.005$, uncorrected) and considered the resultant clusters having >20 voxels to be of some interest if they were located in the regions hypothesized to show less activity in the patient group and/or activated in the controls group in association with PPI.

Neuropsychological measures and their relationship with PPI

The patient and control groups were compared on each neuropsychological variable using independent sample *t* tests. The relationships of mean PPI (averaged across the two SOAs) to neuropsychological variables and symptoms were assessed using Spearman rank correlations (one-tailed test, given previous data from Butler et al., 1991; Karper et al., 1996).

Results

Clinical measures

As shown in Table 1, patients and controls did not differ in age. The symptoms and side-effects ratings in the three patient subgroups were comparable.

Psychophysiological measures

Amplitude and habituation

There was no significant difference between the patients and controls in the amplitude or habituation of the startle response over pulse-alone trials, as there was only a significant effect of block ($F = 13.44$,

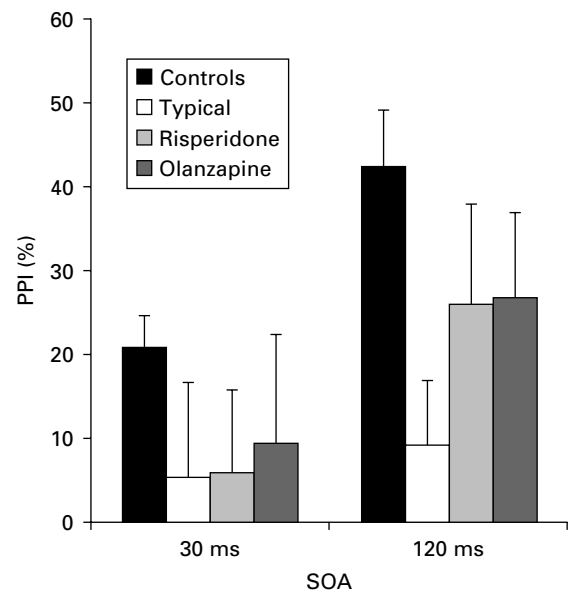


Figure 1. Mean (error bar displays -1 S.E.M.) prepulse inhibition (PPI) of the startle response in groups of controls and patients with schizophrenia classified by medication type. SOA, stimulus onset asynchrony.

$d.f. = 4, 160$, $p < 0.001$) showing habituation of the response over five blocks (linear: $F = 17.62$, $d.f. = 1, 40$, $p < 0.001$), but no diagnosis \times block interaction ($F = 0.03$). The analysis with inclusion of four groups also revealed only a main effect of block ($F = 16.85$, $d.f. = 4, 152$, $p < 0.001$) and no group \times block interaction ($F = 1.24$). Mean (S.D.) startle amplitudes for blocks 1–5 in controls and patients are presented in Table 2.

PPI

There was, as expected, a significant effect of diagnosis ($F = 4.30$; $d.f. = 1, 40$, $p = 0.04$) showing less PPI in patients than controls (Figure 1). There was also a significant effect of trial type ($F = 10.08$; $d.f. = 1, 40$,

$p=0.003$), but no diagnosis \times trial type interaction ($F=0.50$). In the ANOVA involving four groups (controls and three patient subgroups), although the main effect of group was not significant ($F=1.73$, d.f.=3,38, $p=0.18$), planned post-hoc comparisons showed significantly less PPI in the typical antipsychotics group than the control group ($p=0.03$, mean difference 24.51). Those treated with risperidone or olanzapine had apparently reduced PPI relative to controls, but were significantly different neither from controls (risperidone: $p=0.16$, mean difference 15.76; olanzapine: $p=0.22$, mean difference 13.67) nor from patients on typical antipsychotics (risperidone: $p=0.45$, mean difference 8.75; olanzapine: $p=0.35$, mean difference 8.75) (Figure 1). PPI scores were not significantly correlated with symptom ratings (p values >0.20).

Latency to response peak

There was only a trend showing latency facilitation by 30-ms SOA PPI trials relative to the pulse-alone trials (quadratic: $F=3.15$, d.f.=1,40, $p=0.08$) across both groups (F values <1 for group and group \times trial types effects). No other effects were significant.

fMRI

Activation patterns in controls

120-ms SOA PPI > pulse-alone

The strongest activation was seen on the left side in a large cluster with peak activity in the globus pallidus/putamen and extending to caudate, thalamic, insular inferior frontal, temporal, hippocampal, and inferior parietal regions and, on the right side, in a cluster with peak in the inferior parietal region. Another cluster on the right side including parts of the superior temporal gyrus, thalamus and putamen was also activated (Figure 2a, Table 3).

30-ms SOA PPI > pulse-alone

For this contrast, only one cluster in the left temporal gyrus showed some activity (uncorrected for multiple comparisons, Table 3) which extended to parts of the globus pallidus/putamen, thalamus, and hippocampal regions in close proximity to the activations seen for the 120-ms PPI condition.

Activation patterns in patients and comparison with controls

120-ms SOA PPI > pulse-alone

Patients demonstrated activations bilaterally in the temporal lobe which was weaker on the right side but

extended to thalamic and striatal regions (see Figure 2a, Table 3). Activations in some other regions found active in controls were also seen but not significantly so (see Figure 2a).

In the direct comparison of patients with controls, clusters with maximally different activity between the two groups (reduced more in patients than controls) were located in the thalamus (number of contiguous voxels=21; centred at $x=-2$, $y=-6$, $z=10$; $t=2.39$), insular cortex (number of contiguous voxels=79; centred at $x=-40$, $y=-4$, $z=10$; $t=3.18$), and the inferior frontal gyrus (number of contiguous voxels=60; centred at $x=-46$, $y=30$, $z=0$; $t=2.89$) (Figure 2b). Of these three regions, BOLD response in the thalamus (at $x=-2$, $y=-6$, $z=10$) correlated positively with PPI levels across the entire sample ($r=0.36$, $p=0.02$). BOLD responses in other two regions were not significantly correlated with PPI ($p>0.20$).

30-ms SOA PPI > pulse-alone

No region was found to be activated even at the uncorrected (for multiple comparisons) level.

Activation patterns in patients classified by medication type and comparison with controls

Typical antipsychotics group

A large cluster including parts of the anterior as well as posterior cingulate was activated (Table 4). This cluster extended bilaterally to the right temporal gyrus and thalamus but the activations were not strong enough to emerge as areas of sub-peak activity (Table 4). This group showed reduced activity compared to controls in several small clusters (Figure 2c) which did not survive correction for multiple comparisons but were located within the regions found to be activated in association with the 120-ms SOA PPI condition in controls.

Risperidone group

Increased activity was seen in the right superior/middle temporal gyrus extending to the inferior frontal gyrus and striatum. A cluster in the left temporal gyrus, extending to the post-central gyrus and inferior parietal lobe, was also activated (Table 4). This group showed reduced activity in multiple small clusters (Figure 2c) which did not survive correction for multiple comparisons but were located within the regions that had emerged as showing significant activation in association with the 120-ms SOA PPI condition in controls.

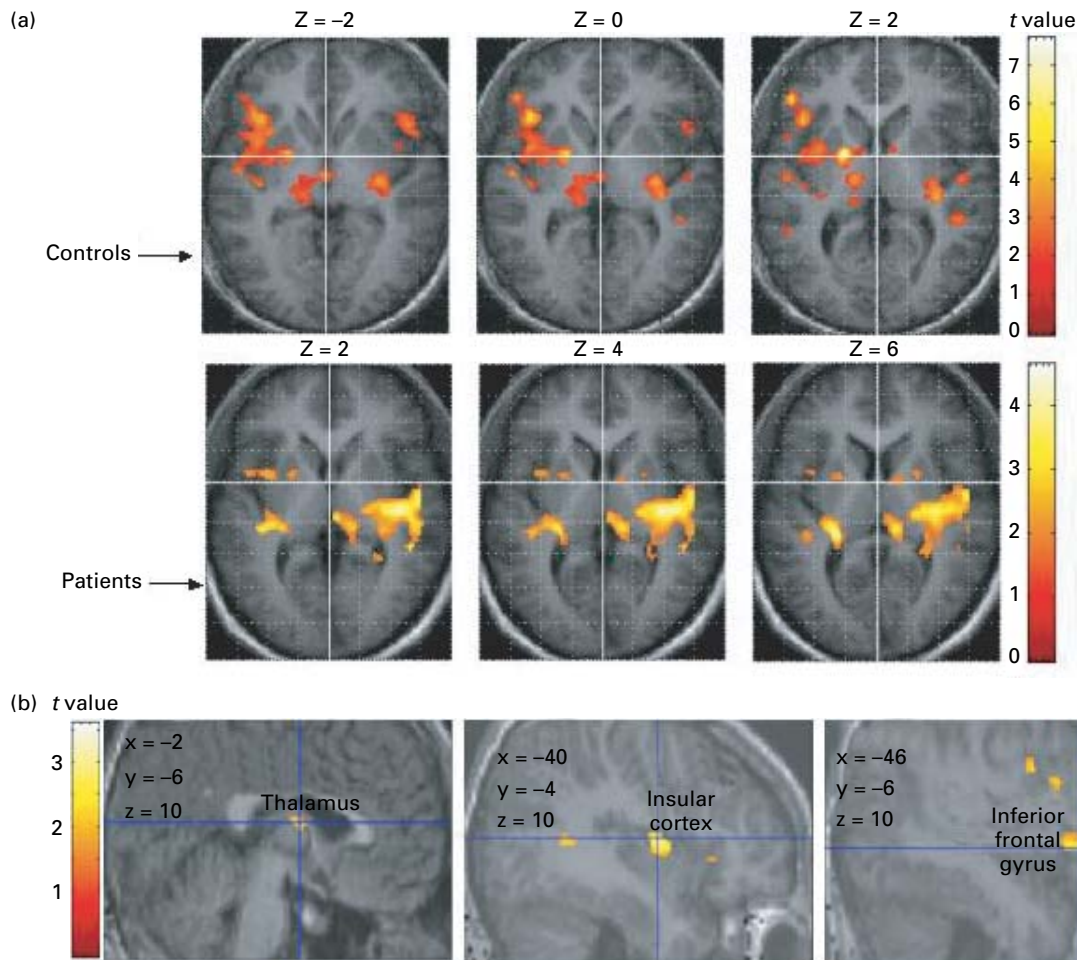


Figure 2. (a) Transverse slices showing regions with a significant response to 120-ms SOA prepulse condition contrasted with the pulse-alone condition in controls (overlaid on the controls' mean structural image) and patients with schizophrenia (overlaid on the patients' mean structural image). (b) Brain areas in sagittal view showing reduced activity in patients compared to controls (overlaid on the patients' mean structural image).

Olanzapine group

The strongest activation was seen in the right superior/middle temporal gyrus. Some activity was seen in the left middle temporal gyrus which extended to the globus pallidus/caudate, hippocampal and thalamic regions. Both pre- and post-central gyrus were also activated. Of the three patient subgroups, activation pattern of this group most resembled to that of controls (Table 4, Figure 2c).

Neuropsychological measures and their association with PPI

As shown in Table 5, patients, on average, showed worse performance than controls on all tests. Reduced PPI in patients was weakly associated with

distractibility on the CPT ($p = 0.06$), significantly associated with the perseverative errors on the WCST ($p = 0.03$) but unrelated ($p = 0.43$) to mental set shifting as assessed by the interference score on the Trail Making Test (see Table 5 for rho values).

Discussion

The main findings of this study were: (i) reduced PPI, on average, in patients with schizophrenia compared to controls, which, when examined according to the medication type, was significantly reduced only in the group treated with typical antipsychotics, (ii) increased brain activity in association with 120-ms PPI in controls in the striatum, thalamus, insula, hippocampal, temporal, inferior frontal and inferior parietal

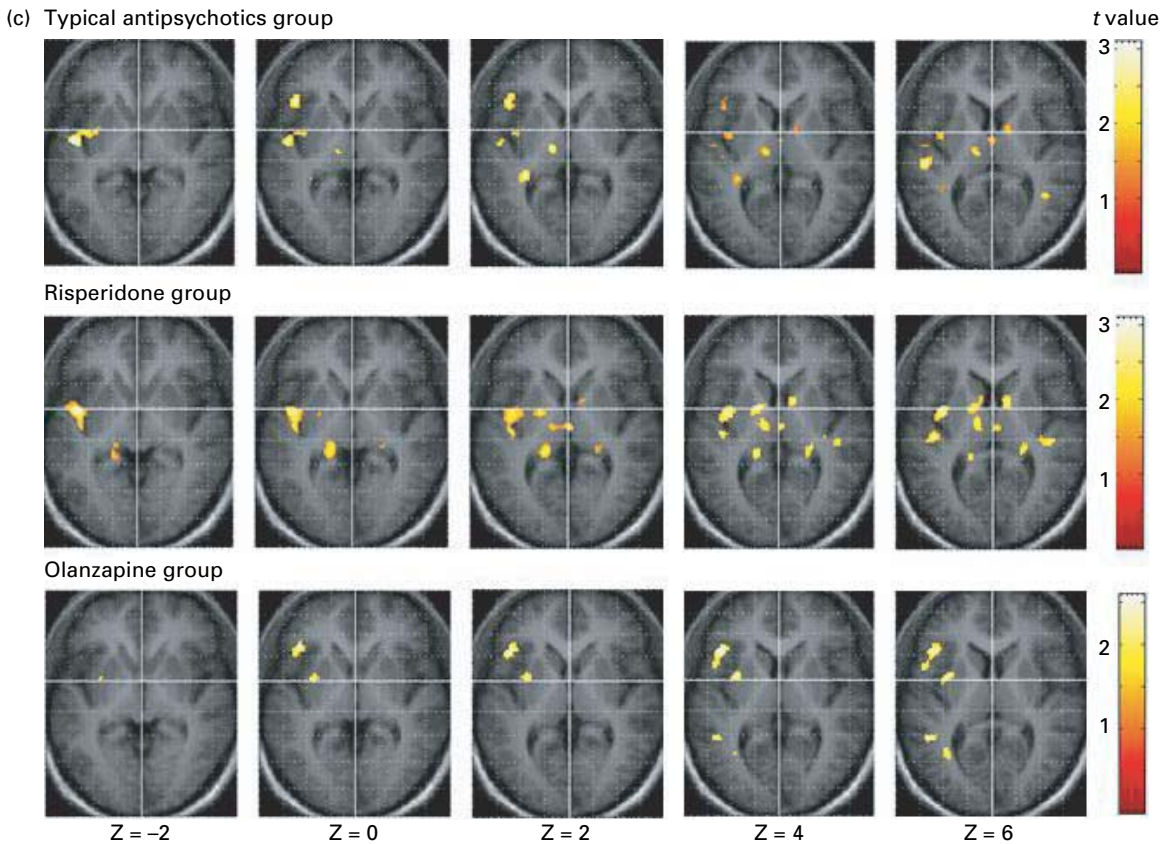


Figure 2 (cont.). (c) Transverse slices showing subtly reduced activity in patients classified by their medication type compared to controls. All images have been thresholded at $p < 0.005$. The colour bars represent the power of activation. The left hemisphere is shown on the left of each slice.

regions, with non-significant increases in the same regions with 30-ms PPI, (iii) reduced fMRI activity in patients, compared to controls, in the thalamic, insular and inferior frontal regions during the 120-ms PPI, of which reduced thalamic activity showed a direct association with PPI across the entire sample, and lastly (iv) when examined according to medication type, reduced fMRI activity, compared to controls, in several small clusters located in the striatal and thalamic regions in the typical antipsychotics and risperidone groups, with relatively fewer such clusters in the olanzapine group.

The observation of reduced tactile PPI in patients compared to controls is well in line with numerous previous reports using acoustic PPI paradigms (see Introduction). This reduction was less pronounced (and non-significant) in patients who had clinically responded and were on stable doses of risperidone or olanzapine. This finding can be taken to suggest that risperidone and olanzapine, like clozapine (Kumari et al., 1999), may have greater PPI-improving effects (than typical antipsychotics) in patients who respond

to these drugs. Atypical antipsychotics are also found in several studies to show greater beneficial effects than typical antipsychotics on cognitive functions (e.g. Keefe et al., 1999, 2004; for reviews see Meltzer and McGurk, 1999; Sharma, 1999), brain activity (Braus et al., 1999; Honey et al., 1999) and brain structural volumes (Corson et al., 1999; Chakos et al., 2005; Garver et al., 2005; Lang et al., 2004; Lieberman et al., 2005). It should be noted, however, that PPI in patients treated with risperidone or olanzapine, although within the normal range, was still somewhat lower than PPI seen in controls. These data, taken together with previous relevant literature, indicate that a graded response, i.e. a progressive increase in PPI from unmedicated patients through those medicated with typical antipsychotics to patients medicated with atypical antipsychotics, occurs in schizophrenia patients. This pattern may be especially strong in those who show responsiveness to a particular drug over a longer period.

The findings of increased activity in the striatum, thalamus, insula, hippocampal, temporal, inferior

Table 3. Clusters showing a significant increase (random-effect model corrected for multiple comparisons, $p < 0.005$ unless indicated otherwise) in BOLD response in association with PPI in controls and patients with schizophrenia

Brain region/structure	Brodmann Area	x, y, z coordinates (mm) for peak and sub-peak activations within the cluster	Side	No. of voxels	t value
Controls (n = 12)					
120-ms SOA > pulse-alone					
Globus pallidus/putamen (extending to thalamic and hippocampal regions)		-20, 2, 4	L	3926	7.79
Middle-superior temporal gyrus	21/22	-50, -32, 4	L		6.13
Inferior parietal lobe	40	-54, -32, 52	L		5.98
Superior temporal gyrus	22	60, -36, 16	R	745*	4.95
Inferior parietal lobe	40	64, -24, 44	R	2129	6.52
30-ms SOA > pulse-alone					
Superior temporal gyrus	22/39	-40, -60, 18	L	1830*	5.26
	22	-50, -38, 10			
Globus pallidus/putamen		-34, -20, 6			
Patients (n = 29)					
120-ms SOA > pulse-alone					
Superior temporal gyrus	22/44	-26, -32, 8	L	3378	4.53
Transverse temporal gyrus	41	-32, 26, 12	L		4.05
Superior temporal gyrus	22/21	-42, -26, 0	L		3.92
Middle temporal gyrus (extends to thalamus)	21	38, -18, 4	R	2113*	4.67
Middle-superior temporal gyrus	21	46, -18, 2	R		4.27
Middle temporal gyrus	21	54, -42, 0			3.77
30-ms SOA > pulse-alone					
No region activated even at the uncorrected level					

BOLD, Blood oxygen level dependent; PPI, prepulse inhibition; SOA, stimulus onset asynchrony; R, Right; L, left.
*Uncorrected.

frontal and inferior parietal regions in association with 120-ms PPI in controls supports the observations of our previous preliminary fMRI study (Kumari et al., 2003) and are consistent with data from animal studies (Swerdlow et al., 2001). The same regions were also activated during the 30-ms PPI condition, but not as robustly, perhaps reflecting the fact that the 30-ms condition elicited less PPI. Patients, on average, showed subtle activation deficits compared to controls in the thalamic, insular, and inferior frontal regions. Patients on typical antipsychotics, who showed impaired PPI, failed to show significant activation in any brain regions that were seen activated in association with PPI in controls. Risperidone- and olanzapine-treated patients showed activation in some PPI-relevant regions, but still had subtle activation deficits in multiple regions. This pattern of differences can be

expected considering the level of observed PPI in these groups.

Reduced PPI in patients was associated with increased perseverative errors on the WCST and increased distractibility on the CPT confirming the observations of Butler et al. (1991) and Karper et al. (1996). However, the strength of these associations was not strong suggesting that only a small percentage of variance in PPI of schizophrenia patients is explained by performance on these neuropsychological tests. Interestingly, impaired PPI in schizophrenia has been reported to be closely associated with severity of thought disorder (Perry and Braff, 1994; Perry et al., 1999). There are previous data indicating an association between impaired executive functioning and presence of a formal thought disorder (Kerns and Berenbaum, 2002, 2003) which, by inference, suggests

Table 4. Clusters showing increased BOLD response (random-effect model, p corrected for multiple comparisons unless indicated otherwise) in patients classified by medication type for the 120-ms SOA PPI condition relative to the pulse-alone condition

Brain region/structure	Brodmann Area	x, y, z coordinates (mm) for peak and sub-peak activations within the cluster	Side	No. of voxels	t value (cluster level p value)
Typical antipsychotics ($n=10$)					
Anterior cingulate	24	-2, 18, 16	L	5943	7.72 (<0.001)
Posterior cingulate	30	-12, -40, 14	L		7.01
	29/30	2, -28, 18	R		5.77
For all other clusters $p > 0.30$ uncorrected					
Risperidone ($n=10$)					
Inferior frontal gyrus		56, -36, 26	R	1624	5.04 (0.012)
Caudate nucleus		18, -6, 26	R		4.89
Superior temporal gyrus	22	36, -20, 4	R		4.54
Superior temporal gyrus	22/42	-46, -38, 20	L	485	3.51 (0.012*)
Inferior parietal cortex	40	-30, -44, 36	L		3.21
Post-central gyrus	2	-40, -26, 34	L		3.18
Inferior frontal gyrus	47	20, 30, -2	R	245	4.56 (0.08*)
	45	28, 34, 16	R		3.56
	45	20, 38, 2	R		3.04
For all other clusters $p > 0.10$ uncorrected					
Olanzapine group ($n=9$)					
Superior temporal gyrus	21/22	44, -12, 6	R	1409	7.62 (0.001*)
	21	58, -12, 6	R		4.61
Middle temporal gyrus	21	46, -30, -2	R		4.28
Parahippocampal gyrus	38	10, -34, -8	R	1304	6.96 (0.001*)
Superior temporal gyrus	21	-48, 8, -8	L		5.08
	22	-52, -4, 0	L		4.39
Precentral gyrus	4	-30, -18, 56	L	633	4.46 (0.018*)
Post-central gyrus	1/2	-52, -20, 46	L		4.13
	4/6	-32, -28, 70	L		4.12
Globus pallidus/caudate		-12, 2, 6	L	296	4.03 (0.09*)

BOLD, Blood oxygen level dependent; PPI, prepulse inhibition; SOA, stimulus onset asynchrony; R, Right; L, left.

*Uncorrected.

that thought disorder may potentially mediate any relationship between reduced neurocognitive performance and reduced PPI in schizophrenia.

Our study has certain limitations. First, we were not able to carry out fMRI and psychophysiological recordings of PPI in the same session although this concern may not be very serious given that PPI has high stability and our imaging findings in controls replicate previous literature on this topic. Second, we used a between-subjects design which is not ideal for examining medication effects. We had originally planned to study patients while they were stable on typical antipsychotics and follow them up for

6 months after they had been switched to olanzapine or risperidone and then compare them with those who remained on typical antipsychotics. In practice, this approach proved difficult because of a rapid change in clinical practice in our study area (i.e. most patients got switched to atypical antipsychotics very quickly, leaving few patients on typical antipsychotics who could be switched to atypicals). Hence, we opted for a between-subjects design in order to include a sufficient number of male patients who were stable and deemed by the treating clinicians to have responded to the typical antipsychotics, risperidone or olanzapine. This design, however, does not permit a definite

Table 5. Specific neuropsychological functions in patients and controls and their relationship to PPI (averaged across 30-ms and 120-ms SOAs) in the patient group

Dependent variable	Controls (<i>n</i> =12) Mean (S.D.)	Patients (<i>n</i> =30) Mean (S.D.)	Group difference		Correlation with PPI in patients	
			<i>t</i> statistic	<i>p</i> value	rho	<i>p</i> value
Sustained Attention: CPT <i>d'</i> ^a	2.28 (1.07)	0.58 (0.55)	6.58	<0.001	0.298	0.065
Mental Flexibility: Trail B-A ^{*b}	29.25 (14.56)	55.93 (50.69)	1.78	0.08	-0.036	0.427
Set-shifting: WCST perseverative errors	10.45 (7.43)	25.63 (17.79)	2.73	0.01	-0.353	0.026

PPI, Prepulse inhibition; SOA, stimulus onset asynchrony; CPT, Continuous Performance Task; WCST, Wisconsin Card Sorting Test.

Numbers reduced to 27^a and 29^b due to two patients' refusal to complete tasks.

* Higher score indicates poor performance.

interpretation of the finding showing significantly reduced PPI in patients on typical antipsychotics but not in patients on atypical antipsychotics as it could reflect some real improvements in PPI with atypical antipsychotics or some uncontrolled clinical bias towards less severe patients chosen to receive such drugs. Third, the typical antipsychotics group included patients on a range of antipsychotics (haloperidol, chlorpromazine and flupenthixol) introducing a potential source of heterogeneity in this group. Although usually classified as typical antipsychotics, these drugs have different receptor profiles (Blin, 1999; Peroutka and Snyder, 1982) and may have differential effects on PPI. Haloperidol acts as a relatively selective D₂ antagonist with moderate affinity for D₃ receptors and low affinities for α_1 and 5-HT_{2A} receptors. Flupenthixol antagonizes both D₂ (high affinity) and D₁ receptors (moderate affinity), and has similar affinities as haloperidol for α_1 and 5-HT_{2A} receptors. Chlorpromazine also antagonizes both D₂ (high affinity) and D₁ receptors (moderate affinity) and, in addition, has moderate affinities for 5-HT_{2A} and cholinergic receptors, high affinity for α_1 receptors and low affinity for histamine₁ receptors. Fourth, our experimental paradigm involved non-random presentation of the stimuli in the box-car design as opposed to random presentation generally employed in startle studies. Nevertheless, blocked presentations of stimuli are found to produce expected neural effects in experimental animals (Humby et al., 1996) and significant activations were found in predicted regions in this study. Finally, the activations showing group differences are very subtle and may represent false positives. Nevertheless, we chose to report them because their locations were consistent with our hypotheses and entertain the possibility that the present sample of patients (all medicated and stable) is

showing a subtle neural deficit rather than no deficit at all. PPI in many patients, although reduced on average compared to controls, was in the normal range under the conditions of the present experiment.

In conclusion, this study confirms the observations of our preliminary fMRI study (Kumari et al., 2003) in showing involvement of thalamic, striatal, temporal and parietal regions in PPI in healthy human subjects and reveals preliminary evidence for a milder PPI deficit and associated brain abnormalities (relative to controls) in patients on stable treatment with atypical antipsychotics, especially olanzapine, than seen in patients on typical antipsychotics.

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Statement of Interest

M.A.G. has an equity interest in San Diego Instruments Inc.

References

- Abel K, Waikar M, Pedro B, Hemsley D, Geyer M (1998). Repeated testing of prepulse inhibition and habituation of

- the startle reflex: a study in healthy human controls. *Journal of Psychopharmacology* 12, 330–337.
- Barnes TRE** (1989). A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 154, 672–676.
- Braff DL, Geyer MA, Swerdlow NR** (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* 156, 234–258.
- Braff DL, Stone C, Callaway E, Geyer M, Glick I, Bali L** (1978). Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 15, 339–343.
- Braus DF, Ende G, Weber-Fahr W, Sartorius A, Krier A, Hubrich-Ungureanu P, Ruf M, Stuck S, Henn FA** (1999). Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. *Schizophrenia Research* 39, 19–29.
- Blin O** (1999). A comparative review of new antipsychotics. *Canadian Journal of Psychiatry* 44, 235–244.
- Butler RW, Jenkins MA, Geyer MA, Braff DL** (1991). Wisconsin Card Sorting deficits and diminished sensorimotor gating in a discrete subgroup of subjects. In: Tamminga CA, Schulz SC (Eds.), *Schizophrenia Research: Advances in Neuropsychiatry and Psychopharmacology*, vol. 1. New York: Raven Press.
- Cadenhead KS, Carasso BS, Swerdlow NR, Geyer MA, Braff DL** (1999). Prepulse inhibition and habituation are stable neurological measures in a normal male population. *Biological Psychiatry* 45, 360–364.
- Chakos MH, Schobel SA, Gu H, Gerig G, Bradford D, Charles C, Lieberman JA** (2005). Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia. *British Journal of Psychiatry* 186, 26–31.
- Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L** (1988). The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Research* 26, 223–238.
- Corson PW, Nopoulos P, Miller DD, Arndt S, Andreasen NC** (1999). Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *American Journal of Psychiatry* 156, 1200–1204.
- Duncan EJ, Szilagy S, Efferen TR, Schwartz MP, Parwani A, Chakravorty S, Madonick SH, Kunzova A, Harmon JW, Angrist B, et al.** (2003a). Effect of treatment status on prepulse inhibition of acoustic startle in schizophrenia. *Psychopharmacology* 167, 63–71.
- Duncan E, Szilagy S, Schwartz M, Kunzova A, Negi S, Efferen T, Peselow E, Chakravorty S, Stephanides M, Harmon J, et al.** (2003b). Prepulse inhibition of acoustic startle in subjects with schizophrenia treated with olanzapine or haloperidol. *Psychiatry Research* 120, 1–12.
- First MB, Spitzer RL, Gibbon M, Williams JBW** (1995). *Structured Clinical Interview for DSM-IV Axis II Disorders, Patient Edition (SCID-P)*, version 2. New York: New York State Psychiatric Institute, Biometrics Research.
- First MB, Spitzer RL, Gibbon M, Williams JBW** (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition (SCID-1/NP)*, version 2. New York: New York State Psychiatric Institute, Biometrics Research.
- Flaten MA** (2002). Test-retest reliability of the somatosensory blink reflex and its inhibition. *International Journal of Psychophysiology* 45, 261–265.
- Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R** (1996). Movement related effects in fMRI time series. *Magnetic Resonance in Medicine* 35, 346–355.
- Friston KJ, Holmes AP, Worsley KJ** (1999). How many subjects constitute a study? *Neuroimage* 10, 1–5.
- Garver DL, Holcomb JA, Christensen JD** (2005). Cerebral cortical gray expansion associated with two second generation antipsychotics. *Biological Psychiatry* 58, 62–66.
- Geyer MA, Ellenbroek B** (2003). Animal behavior models of the mechanisms underlying antipsychotic atypicality. *Progress in Neuropsychopharmacology and Biological Psychiatry* 7, 1071–1079.
- Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR** (2001). Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology* 156, 117–154.
- Graham FK** (1975). The more or less startling effects of weak prestimuli. *Psychophysiology* 12, 238–248.
- Hazlett EA, Buchsbaum MS, Haznedar MM, Singer MB, Germans MK, Schnur DB, Jimenez EA, Buchsbaum BR, Troyer BT** (1998). Prefrontal cortex glucose metabolism and startle eyeblink modification abnormalities in unmedicated schizophrenia patients. *Psychophysiology* 35, 186–198.
- Hazlett EA, Buchsbaum MS, Tang CY, Fleischman MB, Wei TC, Byne W, Haznedar MM** (2001). Thalamic activation during an attention-to-prepulse startle modification paradigm: a functional MRI study. *Biological Psychiatry* 50, 281–291.
- Heaton RK** (1993). *Wisconsin Card Sorting Test*. Psychological Assessment Resources. Florida: Odessa.
- Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T** (1999). Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proceedings of the National Academy of Sciences USA* 96, 13432–13437.
- Humby T, Wilkinson LS, Robbins TW, Geyer M** (1996). Prepulses inhibit startle-induced reductions of extracellular dopamine in the nucleus accumbens of rat. *Journal of Neuroscience* 16, 2149–2156.
- Karper LP, Freeman GK, Grillon C, Morgan 3rd CA, Charney DS, Krystal JH** (1996). Preliminary evidence of an association between sensorimotor gating and distractibility in psychosis. *Journal of Neuropsychiatry and Clinical Neuroscience* 8, 60–66.
- Kay SR, Fiszbein PS, Opler LA** (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13, 261–276.
- Keefe RS, Silva SG, Perkins DO, Lieberman JA** (1999). The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophrenia Bulletin* 25, 201–222.

- Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, et al.** (2004). Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *American Journal of Psychiatry* 161, 985–995.
- Kerns JG, Berenbaum H** (2002). Cognitive impairments associated with formal thought disorder in people with schizophrenia. *Journal of Abnormal Psychology* 111, 211–224.
- Kerns JG, Berenbaum H** (2003). The relationship between formal thought disorder and executive functioning component processes. *Journal of Abnormal Psychology* 112, 339–352.
- Kumari V, Antonova E, Zachariah E, Galea A, Aasen I, Ettinger U, Mitterschiffthaler MT, Sharma T** (2005a). Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans. *Neuroimage* 26, 1052–1058.
- Kumari V, Ettinger U** (2005). Prepulse inhibition deficits in schizophrenia: static or amenable to treatment? In: Lang MV (Ed.), *Progress in Schizophrenia Research*. New York: Nova Publishers.
- Kumari V, Ettinger U, Crawford TJ, Zachariah E, Sharma T** (2005b). Lack of association between prepulse inhibition and antisaccadic deficits in chronic schizophrenia: implications for identification of schizophrenia endophenotypes. *Journal of Psychiatric Research* 39, 227–240.
- Kumari V, Gray JA** (1999). Smoking withdrawal, nicotine dependence and prepulse inhibition of the acoustic startle reflex. *Psychopharmacology* 141, 11–15.
- Kumari V, Gray JA, Geyer MA, ffytche D, Soni W, Mitterschiffthaler MT, Vythelingum GN, Simmons A, Williams SCR, Sharma T** (2003). Neural correlates of prepulse inhibition in normal and schizophrenic subjects: a functional MRI study. *Psychiatry Research: Neuroimaging* 122, 99–113.
- Kumari V, Soni W, Mathew VM, Sharma T** (2000). Prepulse inhibition of the startle response in men with schizophrenia: effects of age of onset of illness, symptoms, and medication. *Archives of General Psychiatry* 57, 609–614.
- Kumari V, Soni W, Sharma T** (1999). Normalization of information processing deficits in schizophrenia with clozapine. *American Journal of Psychiatry* 156, 1046–1051.
- Kumari V, Soni W, Sharma T** (2001). Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Human Psychopharmacology: Clinical & Experimental* 16, 321–326.
- Kumari V, Soni W, Sharma T** (2002). Prepulse inhibition of the startle response in risperidone-treated patients: comparison with typical antipsychotics. *Schizophrenia Research* 55, 139–146.
- Lang DJ, Kopala LC, Vandorpe RA, Rui Q, Smith GN, Goghari VM, Lapointe JS, Honer WG** (2004). Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *American Journal of Psychiatry* 161, 1829–1836.
- Le Pen G, Moreau JL** (2002). Disruption of prepulse inhibition of startle reflex in a neurodevelopmental model of schizophrenia: reversal by clozapine, olanzapine and risperidone but not by haloperidol. *Neuropsychopharmacology* 27, 1–11.
- Leumann L, Feldon J, Vollenweider FX, Ludewig K** (2002). Effects of typical and atypical antipsychotics on prepulse inhibition and latent inhibition in chronic schizophrenia. *Biological Psychiatry* 52, 729–739.
- Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, et al. (HGDH Study Group)** (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry* 62, 361–370.
- Ludewig K, Geyer MA, Vollenweider FX** (2002). Stability of the acoustic startle reflex, prepulse inhibition, and habituation in schizophrenia. *Schizophrenia Research* 55, 129–137.
- Ludewig K, Geyer MA, Vollenweider FX** (2003). Deficits in prepulse inhibition and habituation in never-medicated first-episode schizophrenia. *Biological Psychiatry* 54, 121–128.
- Mackeprang T, Kristiansen KT, Glenthøj BY** (2002). Effects of antipsychotics on prepulse inhibition of the startle response in drug-naïve schizophrenic patients. *Biological Psychiatry* 52, 863–873.
- Meincke U, Morth D, Voss T, Thelen B, Geyer MA, Gouzoulis-Mayfrank E** (2004). Prepulse inhibition of the acoustically evoked startle reflex in patients with an acute schizophrenic psychosis – a longitudinal study. *European Archives of Psychiatry and Clinical Neuroscience* 254, 415–421.
- Meltzer HY, McGurk SR** (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophrenia Bulletin* 25, 233–255.
- Nelson HE, Willison J** (1991). *National Adult Reading Test (NART) Test Manual* (2nd edn). Windsor: NFER-Nelson.
- Ogawa S, Lee TM, Kay AR, Tank DW** (1990). Brain magnetic resonance imaging with contrast dependent blood oxygenation. *Proceedings of the National Academy of Sciences USA* 87, 8868–8872.
- Oldfield RC** (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Oranje B, Van Oel CJ, Gispen-De Wied CC, Verbaten MN, Kahn RS** (2002). Effects of typical and atypical antipsychotics on the prepulse inhibition of the startle reflex in patients with schizophrenia. *Journal of Clinical Psychopharmacology* 22, 359–365.
- Parwani A, Duncan EJ, Bartlett E, Madonick SH, Efferen TR, Rajan R, Sanfilippo M, Chappell PB, Chakravorty S, Gonzenbach S, et al.** (2000). Impaired prepulse inhibition of acoustic startle in schizophrenia. *Biological Psychiatry* 47, 662–669.

- Peroutka SJ, Snyder SH** (1982). Antiemetics: neurotransmitter receptor binding predicts therapeutic actions. *Lancet* 1, 658–659.
- Perry W, Braff D** (1994). Information-processing deficits and thought disorder in Schizophrenia. *American Journal of Psychiatry* 151, 363–367.
- Perry W, Feifel D, Minassian A, Bhattacharjie I, Braff DL** (2002). Information processing deficits in acutely psychotic schizophrenia patients medicated and unmedicated at the time of admission. *American Journal of Psychiatry* 159, 1375–1381.
- Perry W, Geyer MA, Braff DL** (1999). Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. *Archives of General Psychiatry* 56, 277–281.
- Powell SB, Geyer MA** (2002). Developmental markers of psychiatric disorders as identified by sensorimotor gating. *Neurotoxicity Research* 4, 489–502.
- Quednow BB, Wagner M, Westheide J, Beckmann K, Bliesener N, Maier W, Kuhn KU** (2006). Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. *Biological Psychiatry* 59, 536–545.
- Reitan R, Wolfson D** (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. Tucson, AZ: Neuropsychological Press.
- Schwarzkopf SB, McCoy L, Smith DA, Boutros NN** (1993). Test-retest reliability of prepulse inhibition of the acoustic startle response. *Biological Psychiatry* 33, 815–828.
- Sharma T** (1999). The cognitive effects of conventional and atypical antipsychotics in schizophrenia. *British Journal of Psychiatry* 174 (Suppl. 38), 23–30.
- Simmons A, Moore E, Williams SCR** (1999). Quality control for functional magnetic resonance imaging using automated data analysis and showchart charting. *Magnetic Research in Medicine* 41, 1274–1278.
- Swerdlow NR, Braff DL, Taaid N, Geyer MA** (1994). Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. *Archives of General Psychiatry* 51, 139–154.
- Swerdlow NR, Caine SB, Braff DL, Geyer MA** (1992). The neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. *Journal of Psychopharmacology* 6, 176–190.
- Swerdlow NR, Geyer MA** (1998). Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophrenia Bulletin* 24, 285–301.
- Swerdlow NR, Geyer MA, Braff DL** (2001). Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology* 156, 194–215.
- Weike AI, Bauer U, Hamm AO** (2000). Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. *Biological Psychiatry* 47, 61–70.