Psychiatry Research: Neuroimaging 174 (2009) 24–31

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Evidence for reduced somatosensory lateralisation and focalisation in schizophrenia

Thomas P. White[a], Susan T. Francis[b], Verghese Joseph[a], Eileen O'Regan[a], Kay E. Head[b], Peter F. Liddle[a,*]

[a]Division of Psychiatry, School of Community Healthy Sciences, University Park, University of Nottingham, Nottingham, NG7 2UH, United Kingdom
[b]Sir Peter Mansfield Magnetic Resonance Centre, University Park, University of Nottingham, Nottingham, NG7 2RD, United Kingdom

ARTICLE INFO

Article history:
Received 9 July 2008
Received in revised form 9 February 2009
Accepted 15 April 2009

Keywords:
Schizophrenia
fMRI
Lateralisation
Somatosensory

ABSTRACT

Neuroimaging studies indicate diminished lateralisation of cerebral activity during motor tasks and language processing in schizophrenia. Some evidence also indicates that decreased lateralisation is accompanied by more diffuse intra-hemispheric activation, suggesting that diminished lateralisation might be part of a more general diminution of regional functional specialisation. In the case of passive processing of elementary somatosensory stimuli, evidence for decreased lateralisation derived from event-related potential studies, is conflicting. The greater spatial resolution of functional magnetic resonance imaging (fMRI) offers the potential to resolve this conflict. We report an fMRI study of 22 right-handed individuals with schizophrenia, 21 right-handed healthy individuals and 10 non-right-handed healthy individuals, designed to test the hypothesis that in schizophrenia there is a diminution of both lateralisation and intra-hemispheric focalisation during the passive processing of vibrotactile stimuli delivered to the right index finger. Significantly reduced lateralisation of activity in primary somatosensory cortex (SI) was observed in the schizophrenia group as compared to the healthy right-handed group. There was a trend for a reduction in SI lateralisation in the schizophrenia group compared to the healthy non-right-handed group. Contralateral SI focalisation was also significantly reduced in the schizophrenia group compared to both healthy groups. SI focalisation was negatively correlated with severity of disorganisation symptoms in the schizophrenia group. These results support the hypothesis that a generalised loss of functional specialisation is fundamental to schizophrenia.

1. Introduction

Two principles describe the engagement of brain regions for the purpose of processing of information: the principle of regional specialisation states that local brain regions are responsible for specific aspects of processing, while the principle of regional integration states that activity in spatially remote regions must be coordinated if information processing is to produce an effective outcome. Regional specialisation is not immutable. Specialisation tends to be less localised early in development. For example, in early childhood, bilateral motor cortex is active when the child attempts unilateral hand movements (Kinsbourne, 1974), but as the child grows, activity is largely confined to the hemisphere contralateral to the hand that moves. In adult life, damage to a specialised cortical region can result in other brain regions becoming engaged in the task normally performed in the damaged region. For example, following damage to motor cortex (or to related axonal pathways) in one hemisphere, the opposite (ipsilateral) hemisphere tends to be engaged during motor tasks contralateral to the damaged hemisphere (Yoshiura et al., 1997).

It has been proposed that disordered regional integration is a core feature of schizophrenia (Friston, 1998). There is evidence for both abnormally increased and decreased correlations between cerebral activity in spatially separated regions in patients compared with controls (see for example, Honey et al., 2005). Regional integration and regional specialisation are complementary aspects of cerebral organisation and efficient regional integration is likely to require effective specialisation. Abnormal patterns of regional integration might indeed reflect failure of normal regional specialisation. For example, diminished regional specialisation is likely to lead to increased strength of correlation between activity in spatially separate locations.

Imaging studies have provided evidence suggesting diminished regional specialisation in schizophrenia. For example, Mattay et al. (1997) and Bertolino et al. (2004) demonstrated that during hand movement, the degree of lateralisation to the hemisphere contralateral to the moving hand was decreased. Similarly, in the case of language processing, there is evidence for a decrease in the specialisation of the left hemisphere, compared to the strong tendency for lateralisation to the left hemisphere in healthy individuals (Sommer et al., 2003; Weiss et al., 2006). Some evidence suggests that the loss of hemispheric specialisation for language is associated with a more generalised decrease in focalisation of activation within the left hemisphere. For example, in a functional magnetic resonance imaging (fMRI) study of the processing of speech sounds, Ngan et al. (2003) found that in

* Corresponding author.
E-mail address: peter.liddle@nottingham.ac.uk (P.F. Liddle).

0925-4927/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2009.04.004

contrast to healthy individuals, who exhibit a strong left-hemispheric bias to superior temporal gyrus activation, patients with schizophrenia tend to exhibit bilateral activation and display more diffuse activation within the left-hemispheric language areas.

The observation of diminished lateralisation during motor tasks and during language processing demonstrates that decreased lateralisation occurs during processing of information in various different modes. If decreased lateralisation, in particular, and regional specialisation, in general, is a characteristic feature of schizophrenia, it would be anticipated irrespective of the type of information being processed. Both motor tasks and language processing involve a degree of higher-level executive processing, raising the question of whether or not loss of hemispheric specialisation and within-hemisphere focalisation occurs during passive processing of sensory information when executive demands are minimal.

Event-related potential (ERP) studies of somatosensory processing provide conflicting evidence for diminished lateralisation during passive somatosensory processing. Jones and Miller (1981) used an electromagnetic transducer to evoke a somatosensory response in healthy individuals and people with schizophrenia. In healthy individuals they found a P1, N1, and P2 ERP response 22–79 ms post-stimulus that was stronger in amplitude and earlier in the contralateral parietal cortex as compared to the ipsilateral hemisphere. In individuals with schizophrenia no inter-hemispheric amplitude or latency difference was observed. Cooper and colleagues used a modified loudspeaker to replicate this finding and also suggested that disturbances in lateralisation were more common in those individuals exhibiting 'withdrawn' symptoms, which are synonymous with the customary negative symptoms of the disorder (Cooper et al., 1985; Andrews et al., 1986). However, subsequent ERP studies failed to identify disturbed lateralisation of somatosensation in schizophrenia and proposed several misgivings with the previous reports suggesting that misidentification of ERP peaks, variations in electrode placement, and variations in the clinical profiles of the schizophrenia groups in the study by Cooper et al. could have contributed to the conflicting findings of previous studies. The absence of source localisation procedures in all of these previous ERP studies of somatosensation in schizophrenia limits their conclusions.

On account of its superior spatial localisation, fMRI offers the possibility of examining lateralisation and focalisation during somatosensory processing with greater spatial resolution than was feasible in the early ERP studies. We report an fMRI study designed to test the hypotheses that in schizophrenia (i) activation in primary sensory cortex (SI) is less strongly lateralised to contralateral cortex and (ii) activation with the contralateral hemisphere is less tightly localised within the contralateral hemisphere, as compared to healthy subjects.

Crow (1997) has argued that the core feature of schizophrenia involves an abnormality of the hemispheric asymmetry which is characteristic of humans. In particular, in an analysis of birth cohort data, he has found evidence that mixed handedness is associated with increased risk of schizophrenia. Other studies report an increase in left-handedness in schizophrenia, and a meta-analysis of handedness data reveals that both mixed-handedness and exclusive left-handedness have an increased prevalence in schizophrenia (Dragovic and Hammond, 2005). It is plausible that mixed-handedness or left-handedness reflects an abnormality of the development of regional cerebral specialisation. This suggests that the postulated abnormality of lateralisation and focalisation seen in schizophrenia might be related to the process that generates non-right-handedness in the general population. If so, even right-handed patients with schizophrenia might be expected to exhibit patterns of cerebral organisation resembling those seen in non-right-handers in the general population. Therefore, in addition to comparing right-handed patients with schizophrenia with right-handed healthy controls, we have also performed a comparison of patterns of cerebral activity during passive sensory processing in the right-handed patients with that in a group of non-right handed healthy individuals.

2. Methods

2.1. Participants

Twenty-one right-handed healthy individuals (28 ± 8 years, (mean $\pm$ standard deviation)), 22 right-handed individuals satisfying DSM-IV (APA, 1994) criteria for schizophrenia (29 ± 7 years) and 10

Table 1
Participant details.

(A) Demographic data including socioeconomic group as defined by NS-SEC (Rose and Pevalin, 2001); handedness as defined by Annett (1970); current intellectual functioning (QUICK test, Ammons and Ammons, 1962); sex; and ethnicity (http://www.statistics.gov.uk). (Standard deviation in brackets following mean.)

Variable	Healthy right-handed group ($n=21$)	Schizophrenia group ($n=22$)	Healthy non-right-handed group ($n=10$)
	Mean	Mean	Mean
Socioeconomic group	2.2 (1.5)	2.7 (1.6)	1.3 (0.9)
Handedness	10.7 (3.6)	10.2 (1.7)	−9.7 (5.3)
IQ	105.8 (9.1)	100.8 (10.5)	102.6 (7.9)
Sex	18 male, 3 female	19 male, 3 female	8 male, 2 female
Ethnicity	17 White, 3 Mixed, 1 Asian/ British Asian	14 White, 3 Mixed, 2 Asian/ British Asian, 3 Black/British Black	6 White, 2 Mixed, 2 Asian/ British Asian

(B) Medications prescribed to the schizophrenia group ($n=22$) at time of study.

Medication	Number of participants receiving medication
Risperidone	7
Aripiprazole	6
Olanzapine	5
Clozapine	2
Amisulpride	1
Quetiapine	1
Flupenthixol	1
Carbamazepine	1
Venlafaxine hydrochloride	1

(C) Clustered signs and symptoms of psychotic illness (SSPI) `scores for participants in schizophrenia group. (Standard deviation in brackets.)

Symptom cluster	Mean
Psychomotor poverty	2.95 (2.46)
Reality distortion	3.48 (2.16)
Disorganisation	0.48 (0.97)

Table 2
Group mean Talairach coordinates for primary somatosensory (SI) and secondary somatosensory (SII) maxima.

Group	Contralateral SI			Ipsilateral SI			Contralateral SII			Ipsilateral SII		
	x	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
HR ($n=21$)	−57.2 (1.0)	−19.4 (1.3)	50.2 (1.1)	55.2 (1.6)	−20.6 (1.5)	51.4 (1.3)	−60.1 (2.3)	−26.4 (1.8)	22.5 (1.1)	61.5 (2.2)	−22.6 (1.3)	24.4 (1.7)
SZ ($n=22$)	−54.2 (1.5)	−20.2 (1.0)	49.0 (1.2)	56.7 (1.7)	−17.9 (2.0)	52.0 (1.8)	−57.3 (1.5)	−28.0 (1.1)	26.0 (0.8)	52.3 (1.4)	−25.1 (1.0)	22.1 (1.6)
HNR ($n=10$)	−53.8 (2.5)	−16.4 (1.2)	51.4 (1.7)	52.4 (2.1)	−16.9 (1.8)	50.9 (1.3)	−52.9 (1.7)	−26.2 (0.9)	26.8 (1.8)	49.9 (1.1)	−22.6 (1.3)	20.9 (1.5)

Standard deviation in brackets.

non-right-handed healthy individuals (26 ± 6 years) were recruited. Handedness was assessed using the Annett questionnaire (1970). This is a twelve point questionnaire addressing left-right dominance in various motor skills involving the coordination of both upper and lower limb movements. Example questions include the participant being asked which hand they would preferentially use to brush their teeth, and which foot they would favourably use to kick a ball. Groups were mean matched for age, sex, current intellectual function and parental occupation. This information is outlined in Table 1(A).

Patients were recruited during a stable phase of schizophrenia, with stability defined as a change of less than 10 points in their Global Assessment of Function (GAF; DSM-IV; American Psychiatric Association, 1994) score and no changes in type or dose of medication in the six weeks prior to participation in the study. This was achieved via assessment of GAF six weeks prior to participation and immediately prior to participation. Diagnosis was made using DSM-IV criteria on the basis of all available information, including case-file review, clinical interview and consensus meeting between research psychiatrists. All patients were prescribed atypical antipsychotic medication at the time of study, with all medications prescribed for at least six weeks prior to study. Details of these medications are given in Table 1 (B). Equivalent chlorpromazine equivalent doses were computed for oral antipsychotic medication using data presented by Woods (2003). In the case of long-acting risperidone Consta injection, 25 mg Consta injection every 14 days was taken to be equivalent to 4 mg oral risperidone per day, in accordance with the recommendation of the British National Formulary (Joint Formulary Committee, 2008). The presence and degree of psychotic signs and symptoms was assessed using Signs and Symptoms of Psychotic Illness (SSPI) classification (Liddle et al., 2002) within one week of the fMRI session. Results are shown in Table 1(C). Healthy recruits had no history of severe mental illness in a first-degree relative, no personal history of neurological treatment and no currently prescribed medication. Procedures complied with local ethics committee approval. Participants gave informed written consent before taking part.

2.2. Paradigm

A piezoelectric stimulator (T220-H4-503 Standard Brass Shim Bending Element, Piezo Systems, Inc., U.S.A.) was securely attached to the fleshy portion of the distal phalanx of the right index finger for all participants. Somatosensory stimuli were sinusoidal waveforms produced by ICL-8038CCPD (Harris Semiconductor Corp., U.S.A.) precision waveform generators. The four-minute task comprised 14 cycles of a 1 s ON-period and 16 s OFF-period. Event frequency and task length were determined according to a previous study carried out by our group (Francis et al., 2000), in which the parameters used in this study were shown to permit significant BOLD detection in the areas of interest to this study. During the ON-period the stimulator delivered a 100 Hz stimulus of amplitude 100 μm. While several studies (for example, Friston et al., 1999) have suggested that higher experimental efficiency is achieved in randomised rapid-event fMRI, these calculations are based on the detection of the peak of BOLD response. Here we are interested in detecting variations in the haemodynamic response function (amplitude and shape) between brain regions and between participants which are likely to occur in the current sample. This requires good detection of the shape of the HRF including the lower slope of the haemodynamic response in addition to the region near the peak. The 16-second interstimulus interval ensured sufficient return to baseline between stimuli and was in accordance with previous work using the same apparatus. Although this made the occurrence of each stimulus more predictable, this method has proven viable for the localisation of SI and SII (Francis et al., 2000), which was a principal aim of the current study. The participants were instructed that this was a passive task and required no motor response during stimulation. Participants were instructed to stay relaxed but alert between stimulations and to attend to the stimuli when they occurred. For the duration of the paradigm a central fixation cross was presented to the subject using optical-fibre goggles (Avotech, U.S.A.). Participants received no training of the somatic sensation prior to scanning.

2.3. fMRI data acquisition

Scanning was performed on a 3 T Philips Achieva MRI scanner (Philips, Netherlands). Blood oxygenation level-dependent (BOLD) contrast gradient-echo echo-planar images (GE-EPI) were acquired using an eight-channel SENSE head coil with SENSE factor 2 in anterior–posterior direction, TR/TE 1436/35 ms, flip angle 80°, 230×230 mm field of view and 80×80 matrix, with an in-plane resolution of 3 mm × 3 mm and a slice thickness of 4 mm. The TR was selected to ensure that collection of data was jittered over cycles. A single dynamic image comprised 24 contiguous axial slices acquired in descending order. One hundred sixty seven dynamics were acquired during the entire fMRI paradigm.

2.4. Data analysis

2.4.1. Statistical parametric map analysis

fMRI data analysis was performed using SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience,

Table 3
Group mean lateralisation quotient (LQ), focalisation quotient (FQ), and mean maximum *F*-score in primary (SI) and secondary (SII) somatosensory cortices.

Group	SI LQ	SII LQ	SI FQ	Mean maximum *F*-score			
				Contralateral SI	Ipsilateral SI	Contralateral SII	Ipsilateral SII
HR ($n=21$)	0.76 (0.45)	0.51 (0.11)	0.52 (0.09)	5.63 (3.9)	1.98 (1.5)	11.61 (9.3)	7.17 (4.7)
SZ ($n=22$)	0.52 (0.52)	0.46 (0.50)	0.45 (0.11)	4.63 (3.9)	1.82 (0.9)	7.88 (1.8)	4.78 (1.8)
HNR ($n=10$)	0.81 (0.38)	0.55 (0.13)	0.55 (0.40)	10.04 (21.7)	2.41 (2.0)	12.62 (6.7)	6.47 (3.6)

Standard deviation in brackets.

University of London, UK). Data were corrected for slice-timing differences and spatially realigned. Movement parameters were assessed for each participant, with participants excluded from the study if movement exceeded 3 mm. Data were subsequently spatially normalised to the SPM2 EPI template. Spatial smoothing using a Gaussian kernel with 5 mm FWHM was performed and a high-pass temporal filter applied to minimise the effect of low-frequency physiological and scanner-derived confounds.

An event-related analysis was carried out with a general linear model (GLM) design matrix which predicted the time course of the BOLD signal modelled as a 1 s ON-period convolved with the canonical Haemodynamic Response Function (HRF) with temporal derivative, to allow for the possibility of small latency deviations in the activated areas. Realignment parameters were included in the GLM as covariates of no interest. For each individual, statistical parametric *F*-maps (threshold with a false discovery rate (FDR)<0.05) were formed to identify those brain areas associated with somatosensory stimulation. Within-group whole-head analysis was performed for each group to test the null hypothesis that activation did not differ significantly from zero following vibrotactile stimulation. The contrast images created in the single-subject analysis were entered into one-sample *T*-tests.

2.4.2. Lateralisation analysis

Neuronal activation levels vary markedly between individuals (Schlaug et al., 1994; Hasnain et al., 1998). Reports suggest reduced activation levels in psychiatric populations in response to various sensory stimuli (for example, Barch et al., 2003; Perlstein et al., 2003). Therefore for this study it was deemed inappropriate to assess lateralisation for each participant by simply taking the ratio of activated voxels in each hemisphere above a defined threshold level. Our prior hypothesis was of reduced specialisation in S1 and not S2. Performing such an analysis might result in spuriously reduced lateralisation in patients as widespread reductions in activation levels in the schizophrenia group would reduce the number of voxels exceeding a threshold in both hemispheres, in turn resulting in a false pattern of reduced lateralisation in the patient group. Therefore the lateralisation of primary (SI) and secondary (SII) somatosensory responses was evaluated by adapting the ROI-based method of Bertolino et al. (2004) to give a weighted lateralisation quotient (LQ) method using a threshold determined for each individual. Here, rather than defining the ROIs on an individual basis from anatomical data, the method was adapted to use the most activated voxel in SI and SII in an individual's functional data as the centre of the spherical ROIs. In previous studies using this method, ROIs were defined from individual anatomical MRI images, with the primary sensorimotor region defined as the area including the central sulcus, the anterior half of the postcentral gyrus and the posterior half of the precentral gyrus (Mattay et al., 1997; Bertolino et al., 2004). In the current study the loci of the ROIs were defined on an individual basis as there is evidence that inter-subject anatomical variability of functional areas of the order 4–10 mm, dependent on brain region, exists even after spatial normalisation (Fox and Pardo, 1991). Further, anatomy and function of brain regions are not always tightly linked. In this study a focal somatosensory stimulus with a localised response was used. Variation in the anatomical location of maximal SI activation necessitates the use of individual ROIs created on the basis of the functional data. The use of an atlas to delineate ROIs based on Brodmann areas was deemed inappropriate as it was important to dissociate SI and SII. For example, while Brodmann Area 3 primarily incorporates SI and its ventral extent reaches an area which could feasibly include SII activity.

MarsBaR (http://marsbar.sourceforge.net) was used to analyse image intensities within spherical ROIs in the single-subject SPM *F*-maps. For SI, the peak contralateral and peak ipsilateral focus of activation were determined for each participant. The peak SI activation was identified as that closest to the mean location observed in a previous study of healthy subjects using the same piezoelectric stimulation protocol (Francis et al., 2000). ROIs comprised a sphere of 8 mm radius centred on the SI peak focus in each hemisphere. The size of the SI ROI was chosen to reflect the functional extent of this area based on previous work (Francis et al., 2000). The functional extent of SII activation has previously been found to be larger than in SI (Francis et al., 2000). A sphere of 10 mm radius was chosen for SII to match the estimated extent of this functional area. Having defined the ROIs, LQs were calculated for SI and SII using the method of Bertolino et al. (2004) adapted to take into account the locus of the haemodynamic response. First, the mean *F*-value of the 5% of most significantly activated voxels within both the contralateral and ipsilateral ROIs was found. Those voxels whose *F*-value exceeded 50% of this mean *F*-value were considered to be

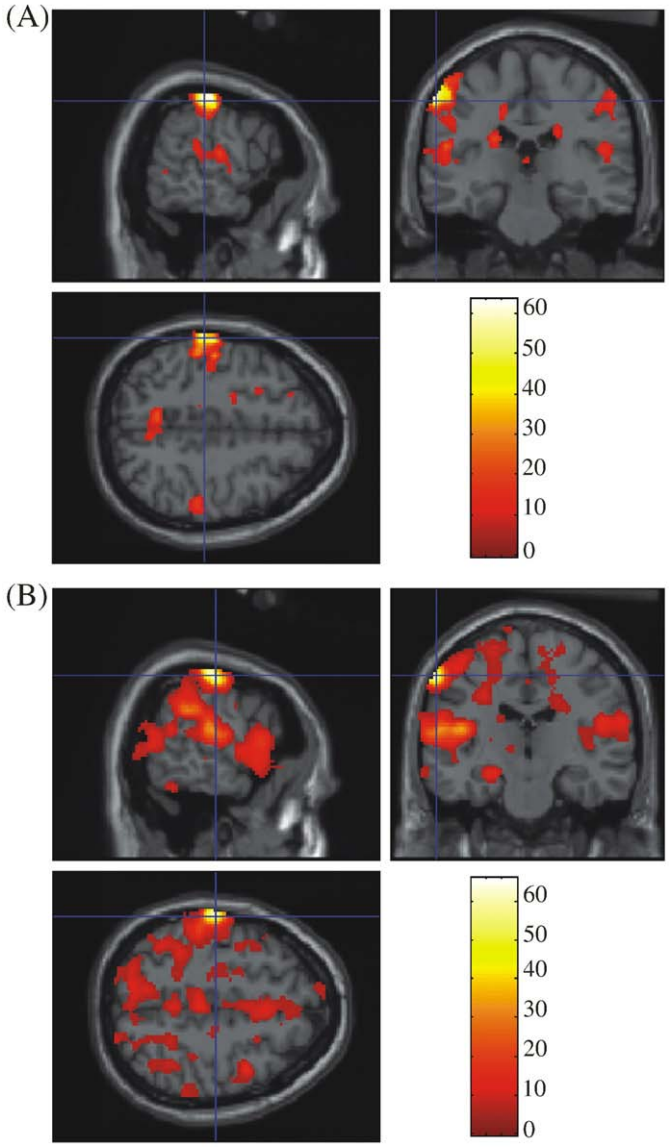

Fig. 1. BOLD responses in (A) a participant with schizophrenia exhibiting reduced lateralisation of response, and (B) a representative right-handed healthy participant showing the typical pattern of lateralisation. Images are displayed for illustrative purposes and with a corrected probability $P<0.05$ FDR. The cross-hair indicates the primary somatosensory cortex. The pseudocolour vertical scales depict *F*-scores. (The apparent widespread activity in the healthy individual response (B) reflects the increased activity level in the healthy individual as compared to the individual with schizophrenia when each subject is shown at the same defined threshold level. This illustrates the need for the use of the Bertolino ROI method to assess lateralisation.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

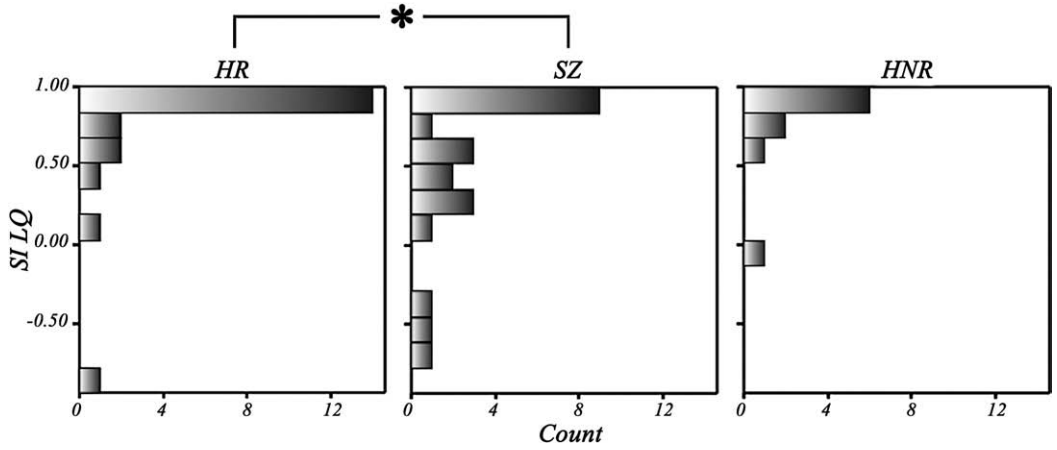

Fig. 2. Histogram of hemispheric specialisation in primary somatosensory (SI) activation in the three participant groups expressed as a lateralisation quotient (LQ). HR, healthy right-handed group; SZ, schizophrenia group; HNR, healthy non-right-handed group. Asterisk denotes between-group difference of $P<0.05$.

active. LQs describing the ratio of significantly active voxels in contralateral and ipsilateral hemispheres were then calculated using:

$$\mathrm{LQ} = \frac{\sum_V X_c - \sum_V X_i}{\sum_V X_c + \sum_V X_i}$$

where V is the number of activated voxels, X_c the F-value of contralateral hemispheric voxels and X_i the F-value of ipsilateral hemispheric voxels. LQ approaches 1 in the limit of dominant contralateral activation and -1 in the limit of dominant ipsilateral activation.

2.4.3. Focalisation analysis

A further analysis was performed to assess whether contralateral SI activation was less focal in the schizophrenia group than the healthy groups. SI identification was accomplished as described above for the lateralisation analysis. MarsBaR was used to identify voxels in two ROIs, the first encompassing a 6-mm radius sphere centred on the voxel of maximum activity and the second a 12-mm radius sphere centred on the voxel of maximum activity. Six mm was chosen given our estimated functional extent of 8 mm for SI. The 6 mm central ROI was expected to capture the peak activation, the 12 mm penumbra ROI was chosen to ensure activation which could feasibly be attributed to SI function was captured, but the ROI was limited to this size to limit noise variance.

The mean F-score from the 6-mm radius ROI was first calculated. By removing the voxels in the 6-mm radius ROI from the 12-mm radius ROI it was possible to generate an ROI in an annulus surrounding the activated area and calculate the mean F-score in this region. Focalisation quotients (FQs) were then calculated as follows:

$$\frac{\mathrm{FQ} = \bar{x}F_c - \bar{x}F_p}{\bar{x}F_c + \bar{x}F_p}$$

where F_c is the mean F-score within the centred 6-mm radius ROI sphere, and F_p the F-score in the annulus. The focalisation analysis was restricted to SI as one would predict a tight spatial focus to activity in this region in healthy individuals. The same prediction would not be made for SII, where diverse higher-order processes contribute to activation on a larger spatial scale.

2.4.4. Relating symptoms of schizophrenia to fMRI measures

Multiple-regression analyses were performed using the enter method. Individual SI and SII LQs and FQs were entered as dependent variables and summed SSPI scores (Liddle et al., 2002) for psychomotor poverty, disorganisation and reality distortion as independent variables. Furthermore, given the hypothesis that disorganisation relates to abnormal localisation of cerebral function (Spitzer, 1997) and so abnormal fMRI responses, a priori planned regression analyses were performed to investigate the relationship between current disorganisation scores and the reported fMRI indices of somatosensation. In addition, regression analyses were performed to assess the relationships of lateralisation and focalisation measures with prescribed equivalent chlorpromazine dosage in the schizophrenia group.

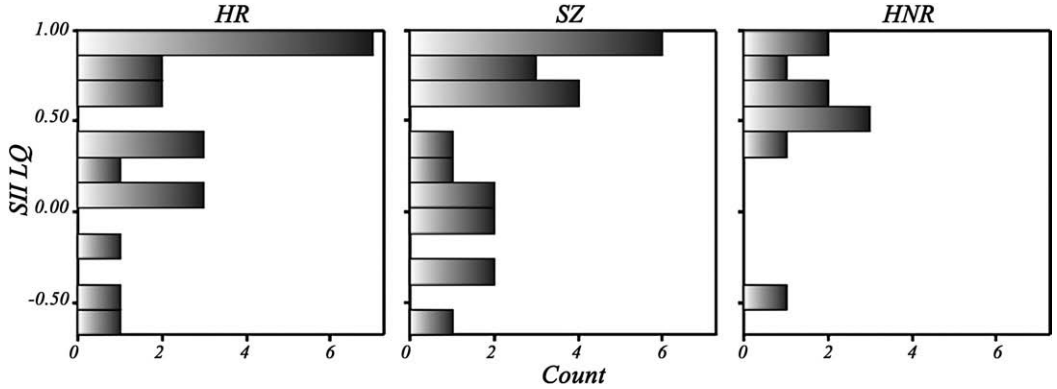

Fig. 3. Histogram of hemispheric specialisation in secondary somatosensory (SII) activation in the three participant groups expressed as a lateralisation quotient (LQ). HR, healthy right-handed group; SZ, schizophrenia group; HNR, healthy non-right-handed group.

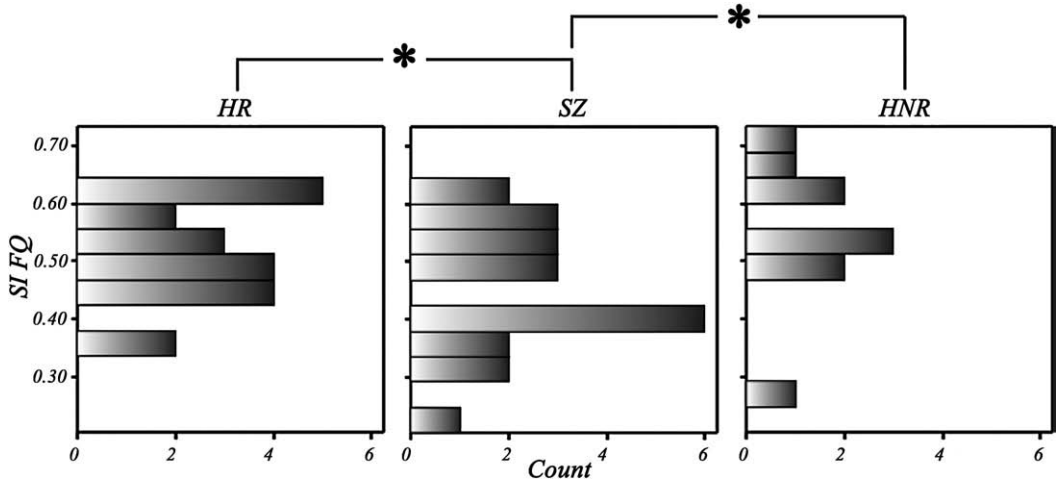

Fig. 4. Histogram of the intra-hemispheric specialisation of primary somatosensory (SI) activation in the three participant groups expressed as a focalisation quotient (FQ). HR, healthy right-handed group; SZ, schizophrenia group; HNR, healthy non-right-handed group. Asterisks denote between-group differences of $P<0.05$.

3. Results

3.1. Lateralisation of SI and SII function

One sample *T*-tests revealed significant SI and SII activity in all groups. Group mean Talairach coordinates for SI and SII maxima are shown in Table 2. LQs and maximum *F*-scores in SI and SII for the three participant groups are given in Table 3. Fig. 1 contrasts the dominant contralateral SI response of a typical healthy right-handed participant with the SI bilateral response evident in several participants of the schizophrenia group. Group maps are not shown as the spatial variation in the SI location obscured in the group maps the statistically significant reductions in hemispheric specialisation evident in the single-subject data. Non-parametric Mann–Whitney *U*-tests of individual LQs revealed the schizophrenia group exhibited diminished SI lateralisation compared to the right-handed healthy group ($P=0.029$). There was also a borderline reduction in the LQs in SI of the schizophrenia group compared to the non-right-handed healthy group ($P=0.059$), but no significant difference between the two healthy groups. Fig. 2 illustrates the distribution of SI LQs scores in the three study groups. Fig. 3 illustrates the distribution of SII LQs in the three study groups. No significant between-group differences in SII lateralisation nor SII maximum *F*-score were observed.

3.2. The focalisation of SI function

Group mean FQs are presented in Table 3. Mann–Whitney *U*-tests revealed that the schizophrenia group FQs were significantly reduced compared to the right-handed ($P=0.026$) and non-right-handed ($P=0.036$) healthy groups. Fig. 4 illustrates the distribution of contralateral SI focalisation in the three study groups. No significant correlation was found between LQs and FQs in any group. It should be noted that the focalisation analysis indicates that there was appreciable signal outside of a 6 mm ROI raising the possibility of appreciable signal outside of the 8 mm ROI employed in the analysis of lateralisation. At least in principle, loss of focalisation might contribute to apparent loss of lateralisation measured within an 8 mm ROI. Retaining a small ROI limits this effect. The absence of a correlation between focalisation and lateralisation index in either the healthy right-handed group ($\rho=-0.147$; $P=0.526$) or the schizophrenia group ($\rho=0.141$; $P=0.532$) suggests that this possible effect was in fact not substantial.

Table 4
Regression analyses of current disorganisation scores and fMRI measures.

fMRI measure	Standardised coefficient (β)	*T*	*P*
SI LQ	−0.74	−0.324	0.749
SII LQ	0.138	0.610	0.549
SI FQ	−0.471	−2.326	0.031*

Asterisk denotes between-group difference of $P<0.05$.

3.3. Symptom-specific analyses

Table 4 details the analyses which tested a priori hypotheses related to symptoms of disorganisation. Current disorganisation scores were found to be a significant predictor of SI focalisation in the schizophrenia group ($R^2=0.22$). Fig. 5 shows a regression plot of this relationship. No other symptom-based analysis produced significant results. Further, SI LQs were not significantly correlated with any symptom measures. No statistically significant relationships were found between any of the fMRI measures and the prescribed equivalent chlorpromazine dosage in the schizophrenia group.

4. Discussion

The major finding of this work was that the schizophrenia group exhibited a significant reduction in SI lateralisation compared to the

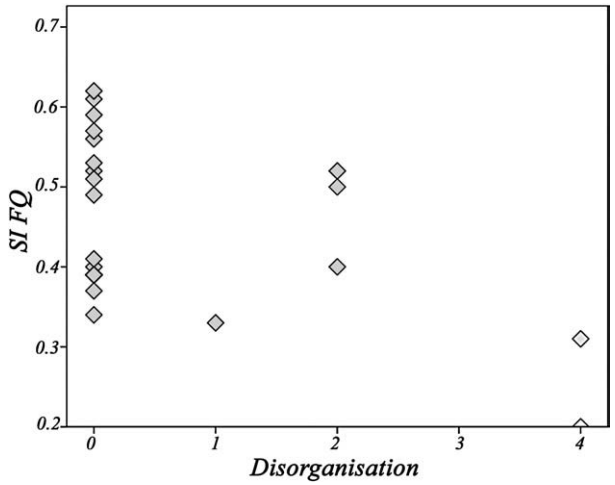

Fig. 5. Regression plot of current disorganisation scores in the schizophrenia group assessed using the Signs and Symptoms of Psychotic Illness (SSPI) questionnaire (Liddle et al., 2002) against intra-hemispheric specialisation of primary somatosensory (SI) activation expressed as a focalisation quotient (FQ).

healthy right-handed group ($P = 0.029$). This finding complements the results of several previous ERP investigations into this phenomenon (Jones and Miller, 1981; Cooper et al., 1985), and coupled with the reductions in functional lateralisation observed in diverse tasks investigating executive (Gonzalez-Hernandez et al., 2003), sensory (Jones and Miller, 1981) and motor functions (Mattay et al., 1997), suggests that schizophrenic disturbances in functional lateralisation transcend language-related abnormalities.

Functional lateralisation has been suggested to originate from inter-hemispheric inhibition during childhood (Kinsbourne, 1974), and to become increasingly evident through adolescence into adulthood. The corpus callosum has been shown to affect this inhibition in the motor system (Ferbert et al., 1992), and similar processes are likely to influence sensory systems, including those responsible for somatosensation. With functional lateralisation increasing during maturation in healthy individuals (Kinsbourne, 1974) and reduced lateralisation common in schizophrenia (for example, Sommer et al., 2003), the current findings support the developmental hypothesis (Weinberger, 1987; Murray and Lewis, 1987). Crow (1997) has advocated transcallosal dysfunction as the mechanism responsible for reduced hemispheric specialisation in schizophrenia, drawing on the finding that individuals at the point of 'hemispheric indecision' (in whom neither hemisphere dominates) tend to perform poorly in linguistic and manual tasks. More specifically, callosal dysfunction has also been suggested to underlie schizophrenia-related differences in somatosensory lateralisation (Jones and Miller, 1981).

The focalisation analysis tested the hypothesis that a lack of hemispheric specialisation in schizophrenia is indicative of a generalised loss of cerebral specialisation. The healthy group expressed a more focused response in contralateral SI than the schizophrenia group (Table 1), suggesting that somatosensory stimuli are processed in a less anatomically-specialised manner in schizophrenia. Such an abnormality might arise from imprecise recruitment of neuronal populations or compensatory processes associated with inefficient neuronal activity. In a working memory study, Tan et al. (2006) reported task-related decreases in dorsolateral prefrontal cortex activation in schizophrenia compared to controls but accuracy-correlated increases in nearby ventral prefrontal regions. It is possible that the current findings are manifestations of similar compensatory processes on a smaller scale. Moreover, Manschreck et al. (1988) and more recently, Spitzer (1997) have proposed that looseness of association, seen by many as a core feature of schizophrenia, results from a spreading of activation from appropriate regions to neighbouring, related but normally inactive, regions of cortex. Although the empirical evidence for Spitzer's hypothesis remains controversial, a study by Moritz et al. (2003) designed to address some of the arguments advanced against Spitzer's hypothesis concluded that the evidence does support the hypothesis that formal thought disorder arises from excessive spreading activation in lexical neighbourhoods. Our observation that decreased focalisation during somatosensory processing is correlated with severity of disorganised mental activity provides indirect support for the proposal that thought disorder arises from excessive spreading cerebral activation.

SII LQs revealed no significant between-group differences. Moreover, SII activation *F*-scores did not significantly differ between any of the groups in either hemisphere. The results presented therefore provide no evidence of SII dysfunction in schizophrenia. This is somewhat surprising given that SII is considered the higher somatosensory cortex, exhibiting differential activity according to attentional and motivational state. However, Liddle et al. (2006) similarly reported no significant SII reductions of the temporo-parietal junction in schizophrenia in response to auditory targets, despite significant clusters of activity in this region in individuals with schizophrenia and healthy participants alike. Nonetheless, Liddle et al. (2006) did report diminished response to targets in numerous association cortex structures in schizophrenia including bilateral intraparietal sulcus.

We found no significant differences between non-right-handers and right-handers in the lateralisation or focalisation during somatosensation, whereas we found that the patients differed from both healthy groups in a broadly similar manner. Thus, we have not found evidence supporting the hypothesis that cerebral organisation in schizophrenia resembles that in non-right-handers, at least within the domain of somatosensation.

A potential task-related limitation of this study is that it involved no measure of behavioural response (because the study was designed to assess perceptual processes with minimal contamination from motor or cognitive processes) and hence produced no index of task performance. It was considered likely that the simplicity and the short length of the task would present little problem to the majority of participants. However, it is possible that medication and psychopathological factors might have reduced attention, arousal and motivation in the patient group and the lower SI *F*-scores might reflect this. However, since highly significant SII activation, indicative of higher-order processing, was apparent in all groups irrespective of diagnosis this suggests that the schizophrenia-related lateralisation and focalisation effects reported here were not simply due to a global reduction in processing in the disorder.

In conclusion, SI lateralisation was reduced in participants with schizophrenia compared to healthy individuals. Furthermore, a tighter spatial focus of contralateral SI activity was observed in healthy individuals compared to schizophrenia participants. The coincidence of these differences suggests that a generalised loss of functional specialisation, rather than a loss of lateralisation or focalisation per se, is fundamental to schizophrenia. Current symptoms of disorganised thought and behaviour in the patients with schizophrenia were found to be correlated with reduced SI focalisation. While this suggests that deficits in the coordination of brain activity and recruitment of task-specific brain structures might underlie observable clinical signs and symptoms of schizophrenia, further study is required to elucidate the precise nature of these relationships.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, 4th ed. American Psychiatric Association, Washington D.C.

Ammons, R.B., Ammons, C.H., 1962. The Quick test. Psychological Test Specialists, Missoula, MT.

Andrews, H.B., House, A.O., Cooper, J.E., Barber, C., 1986. The prediction of abnormal evoked potentials in schizophrenic patients by means of symptom pattern. British Journal of Psychiatry 149, 46–50.

Annett, M., 1970. A classification of hand preference by association analysis. British Journal of Psychology 61 (3), 303–321.

Barch, D.M., Mathews, J.R., Buckner, R.L., Maccotta, L., Csernansky, J.G., Snyder, A.Z., 2003. Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia. NeuroImage 20 (3), 1884–1893.

Bertolino, A., Blasi, G., Caforio, G., Latorre, V., De Candia, M., Rubino, V., Callicott, J.H., Mattay, V.S., Bellomo, A., Scarabino, T., Weinberger, D.R., Nardini, M., 2004. Functional lateralization of the sensorimotor cortex in patients with schizophrenia: effects of treatment with olanzapine. Biological Psychiatry 56 (3), 190–197.

Cooper, J.E., Andrews, H., Barber, C., 1985. Stable abnormalities in the lateralisation of early cortical somatosensory evoked potentials in schizophrenic patients. British Journal of Psychiatry 146, 585–593.

Crow, T.J., 1997. Is schizophrenia the price that *Homo sapiens* pays for language? Schizophrenia Research 28 (2–3), 127–141.

Dragovic, M., Hammond, G., 2005. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatrica Scandinavica 111, 410–419.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., Marsden, C.D., 1992. Interhemispheric inhibition of the human motor cortex. Journal of Physiology 453, 525–546.

Fox, P.T., Pardo, J.V., 1991. Does inter-subject variability in cortical functional organisation increase with neural 'distance' from the periphery? In: Chadwick, D.J., Whelan, J. (Eds.), Exploring brain functional anatomy with positron emission tomography. . Ciba Foundation Symposium, vol. 163. John Wiley & Sons, Chichester, pp. 125–145.

Francis, S.T., Kelly, E.F., Bowtell, R., Dunseath, W.J., Folger, S.E., McGlone, F., 2000. fMRI of the responses to vibratory stimulation of digit tips. NeuroImage 11 (3), 188–202.

Friston, K.J., 1998. The disconnection hypothesis. Schizophrenia Research 30 (2), 115–125.

Friston, K.J., Zarahn, E., Josephs, O., Henson, R.N., Dale, A.M., 1999. Stochastic designs in event-related fMRI. NeuroImage 10 (5), 607–619.

Gonzalez-Hernandez, J.A., Pita-Alcorta, C., Cedeno, I., Dias-Comas, L., Figueredo-Rodriguez, P., 2003. Abnormal functional asymmetry in occipital areas may prevent

frontotemporal regions from achieving functional laterality during the WCST performance in patients with schizophrenia. Schizophrenia Research 61 (2–3), 229–233.
Hasnain, M.K., Fox, P.T., Woldorff, M.G., 1998. Intersubject variability of functional areas in the human visual cortex. Human Brain Mapping 6, 301–315.
Honey, G.D., Pomarol-Clotet, E., Corlett, P.R., Honey, R.A., McKenna, P.J., Bullmore, E.T., Fletcher, P.C., 2005. Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. Brain 128 (11), 2597–2611.
Joint Formulary Committee, 2008. British National Formulary, 56th ed. British Medical Association and Royal Pharmaceutical Society of Great Britain, London.
Jones, G.H., Miller, J.J., 1981. Functional tests of the corpus callosum in schizophrenia. British Journal of Psychiatry 139, 553–557.
Kinsbourne, M, 1974. Cognitive deficit and the aging brain: a behavioral analysis. International Journal of Aging and Human Development 5 (1), 41–49.
Liddle, P.F., Laurens, K.R., Kiehl, K.A., Ngan, E.T., 2006. Abnormal function of the brain system supporting motivated attention in medicated patients with schizophrenia: an fMRI study. Psychological Medicine 36 (8), 1097–1108.
Liddle, P.F., Ngan, E.T., Duffield, G., Kho, K., Warren, A.J., 2002. Signs and Symptoms of Psychotic Illness (SSPI): a rating scale. British Journal of Psychiatry 180, 45–50.
Manschreck, T.C., Maher, B.A., Milavetz, J.J., Ames, D., Weisstein, C.C., Schneyer, M.L., 1988. Semantic priming in thought disordered schizophrenic patients. Schizophrenia Research 1 (1), 61–66.
Mattay, V.S., Callicott, J.H., Bertolino, A., Santha, A.K., Tallent, K.A., Goldberg, T.E., Frank, J.A., Weinberger, D.R., 1997. Abnormal functional lateralization of the sensorimotor cortex in patients with schizophrenia. Neuroreport 8 (13), 2977–2984.
Moritz, S., Woodward, T.S., Küppers, D., Lausen, A., Schickel, M., 2003. Increased automatic spreading of activation in thought-disordered schizophrenic patients. Schizophrenia Research 59 (2–3), 181–186.
Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? British Medical Journal 295 (6600), 681–682.
Ngan, E.T., Vouloumanos, A., Cairo, T.A., Laurens, K.R., Bates, A.T., Anderson, C.M., Werker, J.F., Liddle, P.F., 2003. Abnormal processing of speech during oddball target detection in schizophrenia. NeuroImage 20 (2), 889–897.
Perlstein, W.M., Dixit, N.K., Carter, C.S., Noll, D.C., Cohen, J.D., 2003. Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. Biological Psychiatry 53 (1), 25–38.
Rose, D., Pevalin, D.J., 2001. The national statistics socio-economic classification: unifying official and sociological approaches. Institute of Social Economic Research Papers.
Schlaug, G., Knorr, U., Seitz, R.J., 1994. Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. Experimental Brain Research 98, 523–534.
Sommer, I.E., Ramsey, N.F., Mandl, R.C., Kahn, R.S., 2003. Language lateralisation in female patients with schizophrenia: an fMRI study. Schizophrenia Research 60 (2–3), 183–190.
Spitzer, M., 1997. A cognitive neuroscience view of schizophrenic thought disorder. Schizophrenia Bulletin 23 (1), 29–50.
Tan, H.Y., Sust, S., Buckholtz, J.W., Mattay, V.S., Meyer-Lindenberg, A., Egan, M.F., Weinberger, D.R., Callicott, J.H., 2006. Dysfunctional prefrontal regional specialisation and compensation in schizophrenia. American Journal of Psychiatry 163 (11), 1969–1977.
Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry 44 (7), 660–669.
Weiss, E.M., Hofer, A., Golaszewski, S., Siedentopf, C., Felber, S., Fleischhacker, W.W., 2006. Language lateralisation in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. Psychiatry Research 146 (2), 185–190.
Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. Journal of Clinical Psychiatry, 64 (6), 663–667.
Yoshiura, T., Hasuo, K., Mihara, F., Masuda, K., Morioka, T., Fukui, M., 1997. Increased activity of the ipsilateral motor cortex during a hand motor task in patients with brain tumor and paresis. American Journal of Neuroradiology 18 (5), 865–869.