Abstract:

Delusions and hallucinations are classic positive symptoms of schizophrenia. Contemporary cognitive theories suggest that the misattribution of self-generated actions may underlie these symptoms. However, there are very few longitudinal functional imaging studies investigating neural activation associated with change in symptoms.

We studied brain activation using functional magnetic resonance imaging (fMRI) during a motor task in 11 patients with schizophrenia and 9 healthy controls. The patient group was tested at two time points separated by 6-8 weeks. At initial testing, the patient group had a mean Positive and Negative Syndrome Scale score of 56.3, and showed significantly increased activation within the left inferior parietal lobe (IPL) compared to controls. Patients reported significantly decreased positive symptoms at 6-8 week followup and IPL activation had returned to normal. Our results demonstrate that first-rank positive symptoms are associated with hyperactivation in the secondary somatosensory cortex (IPL). These findings lend further credence to the theory that a dysfunction in the sensory feedback system underlying our sense of agency may contribute to the aetiology of first-rank symptoms.

Background:

Hallucinations and delusions are hallmark symptoms of schizophrenia. A contemporary model, the forward output model (see Frith 2005), proposes that these symptoms arise from a dysfunction of the patient’s internal 'self-monitoring' (Frith 1992; Franck et al. 2002). Normally, a self-generated action produces an internal efference copy. The efference copy is used in conjunction with an internally represented causal model linking actions to their sensory outcomes to give a prediction of the sensory consequences of our actions (Blakemore et al. 2000; Frith 2005). According to this model, patients with hallucinations and delusions (particularly delusions of control) fail to integrate the intention to move, and the perception of their action e.g. their limb moving, and do not consider themselves as the originator of the action and thus failure of this internal model has the consequence of the action being assigned to an external agency; the belief being that someone else has caused their limb to move.

Forward output model theories claim that when an action is identified as our own, its sensory consequence is pre-attentionally attenuated (Shergill et al., 2003; Frith, 2005). Patients fail to identify their actions in this way and consequently show less attenuation. Supporting this, patients have been found to demonstrate significantly less attenuation than healthy controls in behavioural studies (Milne et al., 1988; Blakemore et al. 2000a; Blakemore et al., 2000b; Knoblich et al., 2004; Frith, 2005; Shergill et al., 2005). In an earlier study, we demonstrated that patients with a diagnosis of schizophrenia applied less force than controls when asked to match a given level of force directly; while both groups were equally accurate in their application of matched given force when done indirectly, using the joystick (Shergill et al. 2005). This was in accordance with a model whereby the improved accuracy of the patient group in the direct task is secondary to lower levels of sensory attenuation contingent on dysfunctional feed forward modelling of direct self-generated actions.

Correspondingly, one would expect patients to reflect this reduction in attenuation by presenting changes in neuronal activation related to sensory feedback. In the case of a motor task, one could expect to see abnormal activation in the somatosensory cortex, since this region is believed to be responsible for processing tactile stimuli. This prediction has been met by a number of previous studies of motor tasks in patients (Spence et al. 1997; Blakemore et al., 2003; Farrer et al. 2004; Ganesan et al. 2005; Schnell et al. 2008), which have reported hyperactivation in the inferior parietal lobe (Brodmann Area 40), which includes the secondary somatosensory cortex. However, there are few such studies of longitudinal functional imaging studies investigating cortical changes associated with psychosis and motor action. Of these, most have used PET (for example Spence et al. 1997; Farrer et al. 2004). Only a couple have used fMRI (Ganesan et al., 2005; Schnell et al. 2008). fMRI has a number of advantages over PET,
including safety considerations, which allow for a larger number of images to be acquired in a single session, and scope for an event-related design (Amaro et al., 2002), thereby substantially increasing sensitivity.

We used fMRI to examine brain activation in 11 patients during a motor task modified from Spence et al. (1997). We imaged patients at two time points 6 to 8 weeks apart, keeping medication stable, and measured changes in symptoms scores over time – and a group of 9 controls on one occasion. Our hypothesis was that patients would show increased IPL activation relative to healthy controls at baseline and that this activation would show an inverse relationship with their positive symptom levels over time.

Methods:

Participants:

11 patients (nine males, two females) diagnosed with DSM-IV schizophrenia were recruited (mean age 35.4 years (SD 9.2), years in full-time education 13.5 (SD 2.1), duration of illness 12.6 years (SD 9.1), NART IQ 106.9 (SD 11.0)). All were receiving stable doses of antipsychotic medication; mean dose was chlorpromazine equivalent of 523mg/day (SD 455mg; eight treated with conventional and three with atypical antipsychotics). The interval between the initial and follow up measurements was 6 to 8 weeks, considered sufficient to allow for change in positive symptoms, and antipsychotic medication was kept constant. Two patients failed to attend for their second scan and so were excluded from the analysis.

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) immediately prior to scanning on both occasions. The mean total score was 56.3 (SD 16.5) at the initial scan and 48.3 (SD 6.6) at follow up with mean positive PANSS scores of 15.4 (SD 6.7) at the initial scan and 11.4 (SD 4.1) at follow up. The difference between scanning sessions was significant for the positive symptoms (t(8)=2.33, P=0.048), but not for the total score (t(8)=1.68, P=0.13).

9 healthy control participants were scanned once. Complete data were not available for one participant due to technical problems, and so he/she was excluded from subsequent analysis. The control subjects (five males and three females) were comparable to the patients for age (mean 33.3 years; SD 7.2, t(16)=0.50, P=0.62) and education (mean 15.7 years; SD 3.1 t(16)=1.78, P=0.09).

Controls were excluded if they had a history of drug or alcohol abuse, neurological illness, head injuries, speech or hearing difficulties, or any contraindications to MRI scanning such as metal implants. All subjects provided informed consent, and ethical approval was obtained from the Institute of Psychiatry Ethics Committee.

Task:

The motor task we used during the experiment was based closely on that used by Spence et al. (1997). Participants held a joystick in their right hand and looked at a computer screen being reflected in a mirror contained in a head cage used during scanning. The task comprised three conditions: a cued condition, a spontaneous condition, and a rest condition. Each trial lasted a total of 6 seconds, comprising a 1 second presentation of the cue, followed by a 3 second response time, and a 2 second wait with a fixation cross before the next trial. Each condition was featured 20 times during the task and in randomised order, lasting for 6 minutes in total.

In the cued condition, participants were directed by a cue to move the joystick in a specific direction. A red dot, positioned in one of four possible positions (up, down, left, right), was presented on the screen. After a delay of one second the dot turned green and the participant moved the joystick in the direction corresponding to its onscreen position.

In the spontaneous condition, four red dots were presented on the screen simultaneously and once they turned green the participant moved the joystick in a direction of their choice. Participants were asked not to pre-plan their action.

The rest condition, also occurring twenty times, required the participants to stare at a fixation cross appearing on the screen without performing any movement. This condition was used as a low-level baseline during the data analysis.

Data acquisition:

Data were acquired using a 1.5 Tesla GE Signa Neuro-optimized MR System (GE, Milwaukee, WI, USA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for RF transmission and reception. Two hundred and forty T2*-weighted gradient echo planar images depicting blood-oxygen-level-dependent (BOLD) contrast were acquired from 16 non-contiguous planes parallel to the anterior commissure-posterior commissure plane [slice thickness 7.7 mm, slice gap 0.7 m, repetition time (TR) 2 s, echo time (TE) 40 ms, flip angle = 90°]. A high-resolution inversion recovery echo-
planar image of the whole brain was also obtained [TE = 73 ms, inversion time (TI) = 180 ms, TR = 16 s] for subsequent registration to the standard stereotaxic space of Talairach and Tournoux (1998).

Image analysis:

Data were analysed with the XBAM software developed at the Institute of Psychiatry, London, using a non-parametric approach (for a full description and references see http://www.brainmap.it). Experimental responses were analysed by convolving each component of the experimental design with each of two gamma variate functions (peak responses at 4 and 8 seconds respectively). The best fit between the weighted sum of these convolutions and the time series at each voxel was computed. Following this, a goodness of fit statistic was computed. This consisted of the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) due to the model to the sum of squares of deviations due to the residuals (sum of squares [SSQ] ratio). The data were then permuted using a wavelet-based method. In addition to the SSQ ratio, the size of the BOLD response to each experimental condition was computed for each individual at each voxel as a percentage of the mean resting image. Within group comparisons of experimental conditions to each contrast of interest were then computed separately for the patient and the control group. The observed and permuted SSQ ratio maps for each individual, as well as the BOLD effect size maps, were transformed into standard space using a two-stage warping procedure. Group activation maps were then computed by determining the median SSQ ratio at each voxel (over all individuals) in the observed and permuted data maps (medians are used to minimize outlier effects). The distributions of median SSQ ratios over all intracerebral voxels from the permuted data were then used to derive the null distribution of SSQ ratios. Cluster level maps for both between and within group analyses were thresholded at < 1 expected type I error 3D cluster per brain. As the cluster level threshold is set at the whole brain level, the normal, voxelwise issue of multiple comparisons does not apply. Comparisons of responses between groups or experimental conditions were performed using non-parametric analysis of variance (ANOVA). Data were fitted at each intracebral voxel at which all subjects have non-zero data using a linear model of the type \( Y = a + bX + e \), where \( Y \) is the vector of BOLD effect sizes for each individual, \( X \) is the contrast matrix for the particular intercondition/group contrasts required, \( a \) is the mean effect across all individuals in the various condition/group, \( b \) is the computed group/condition difference and \( e \) is the vector of residual errors. The model is fitted by minimizing the sum of absolute deviations rather than the sums of squares to reduce outlier effects. The null distribution of \( b \) is computed by permuting data between conditions (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model. Group difference maps were computed as described above at cluster level by appropriate thresholding of the null distribution of \( b \), to give less than one false positive 3D cluster per image. This is a standard method for tests of this kind and it gives exact \( P \) values with minimum assumptions.

Results:

Group maps were produced for each task for all three groups – controls, patients at T1, and patients at T2. The results showed heightened activity in the left IPL (BA 40) in patients at T1 during both cued (cluster size=3372, \( p=0.0004 \)) and spontaneous tasks (cluster size=3470, \( p=0.0003 \)). Activity was also detected in the left Primary Somatosensory Cortex (BA 3) for controls during both tasks.

ANOVAs were performed contrasting the cued and spontaneous tasks for each of the three groups. Maps were also contrasted between groups (patients at T1 vs. controls, patients at T2 vs. controls, and patients at T2 vs. T1) for a total of 9 comparisons.

Patients at T1 demonstrated greater activation in the left IPL (BA 40) compared to both T2 (cluster size=127, \( p=0.0037 \)) and the control group (cluster size=119, \( p=0.0039 \)) during the spontaneous task, but not during the cued task. Greater left IPL activity in the same region was also detected during the spontaneous task compared to the cued task for both the patients at T1 (cluster size=66, \( p=0.0094 \)) and the control group (cluster size=416, \( p=0.0002 \)). Heightened activity was also found in the left Primary Somatosensory Cortex (BA3) in controls compared to patients at T1 in both tasks (cluster size=90, \( p=0.0031 \) and cluster size=167, \( p=0.0029 \)).

Conclusions:

We tested for differences over time in patients with schizophrenia and a group of healthy control subjects, during a cued and spontaneous motor task. We found that when the patients’ PANSS scores were maximal, they showed hyperactivation of the left inferior parietal lobule (BA 40) during the spontaneous condition compared to both the cued task and the other
participant groups, this normalised with the patients’ decrease in symptoms over time. These results are consistent with those from previous studies (Spence et al 1997), and match our expectations of the IPL’s involvement in the visuomotor network.

According to Frith (2005), for the forward output model ‘any predictable signal has less impact on the nervous system (unless it has some special a priori value).’ Under such circumstances, the forward output model therefore suggests that a predictable outcome will elicit lower levels of neuronal activation in the relevant cortical region(s). We tested this hypothesis by asking participants to perform both cued and spontaneous motor tasks. The cued tasks are believed to offer greater predictability than the spontaneous tasks in terms of the expected sensory outcome they will elicit for the participants, because participants hold in their working memory the nature and direction of the arm movement beforehand. The spontaneous tasks meanwhile are intended to minimise future planning, and so correspondingly minimise predictability for the participants. Our results appear to be consistent with this expectation. The spontaneous task consistently elicited greater levels of neuronal activation in the IPL than the cued task.

The comparison of spontaneous tasks between patients when their PANSS were maximal (time 1) and at a later date with lower PANNS scores showed that the IPL was most active at time 1, while there was no significant difference in cortical activation between controls and patients at time 2. According to the forward output model, this can be explained as a reduction in cortical attenuation. Frith (1992) suggests that certain passivity phenomena, such as auditory hallucinations and delusions of control, could be caused by a failure in our normal internal self-monitoring processes. Ordinarily when we act, an efference copy is produced at the initiation of the action. When an outcome signal, such as the somatosensory feedback from moving a joystick, differs from the efference copy produced at its origin, the outcome signal is not matched to our own action, and the signal is not attenuated. Correspondingly, the sensory outcome of that action is not identified as being initiated by ourselves. As such, even though it was in fact our own action, it is experienced as both having greater sensory outcome intensity than is normal for an action we initiate, and also as if it has originated from an external agency. Our results corroborate this model by showing an apparent link between increased activation in the IPL and increased positive symptoms.

Our findings further demonstrate that IPL hyperactivation is systematically found in patients with positive symptoms of psychosis while performing motor activity. However, while we observed left hemisphere hyperactivation, most studies have implicated the right hemisphere instead (e.g. Spence et al. 1997). Our findings indicate that first-rank symptoms may not be specifically associated with right IPL hyperactivation during motor tasks, but that the hemispherical location may be more complex. It could be argued that these studies typically enrol patients specifically with delusions of control as their test participant group, and that the difference in patient group may be responsible for the difference in results. However, evidence for right hemisphere specificity comes from a range of patient groups specifically reporting psychotic symptoms, and is not restricted to patients reporting delusions of control (e.g. Ishii et al., 2007). Meanwhile, Ganesan et al. (2005) also enrolled patients diagnosed with schizophrenia and reporting high PANSS scores, but not specifically delusions of control, and reported right hemispherical hyperactivation of the IPL. Therefore, the difference in hemispherical location is unlikely to be due to the patient group. In addition we are not alone in finding hyperactivation either bilaterally or in the left IPL (e.g. Spence et al., 1997; Blakemore et al., 2003; Schnell et al., 2008). Therefore, it is doubtful that the choice of patient group can account for the difference in hemispherical location, while bilateral involvement is a more reasonable conclusion.

Possible limitations for this study include the generalisability of our results, since our patient and control groups both included relatively small numbers. However, we used a non-parametric statistical approach as well as stringent thresholds for all of our analyses to minimize any Type I errors. Secondly, we cannot account for test–retest effects since the control group was scanned only once, although previous studies have not reported test-retest effects in the IPL (Spence et al. 1997). A significant correlation between drop in patients’ PANSS scores, and particularly in the positive items, with change in IPL activation would help address this concern. However, regression analysis did not indicate a significant direct correlation between changes in symptom level and neuronal activation between scanning sessions; this could be a consequence of limited variance in the symptom change. This leaves open the possibility that changes in brain activation between study entry and endpoint in the patient group can be attributed both to changes in clinical state and test-retest effects. However, differences over time were greater in the spontaneous task — which could argue against any non-specific effects of repetition. The strength of this study is that medication was kept constant throughout our study.. Finally, the assumption regarding the functional difference between cued and
spontaneous tasks could have been tested further. Since both tasks feature self-generated movement, they both have an element of predictable sensory feedback signals. Future studies could usefully create a parameterised differential in the predictability between tasks.

In summary, our findings demonstrate that positive psychotic symptoms are associated with hyperactivity of the left IPL during spontaneous motor activity. This evidence provides further support for the forward output model, and so indicates the importance of this theory in our understanding of the aetiology of schizophrenia.
References:


Figure 1 Ascending transverse sections through the brain from left to right, relative to the intercommissural plane (mm). The right side of the brain is shown in the left side of each image. The red clusters illustrate increased brain activation (in red) during the spontaneous task for row a) patients at T1 compared to controls and row b) patients at T1 compared to T2 in each of the images. In each case, the activation is located in BA40.