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Keywords

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Abstract

Background - Superior temporal lobe dysfunction is a robust finding in functional neuroimaging studies of schizophrenia, and is thought to be related to a disruption of fronto-temporal functional connectivity. However the stage of the disorder at which these functional alterations occur is unclear. We addressed this issue by using functional MRI (fMRI) to study subjects in the prodromal and first episode phases of schizophrenia.

Methods - Subjects with an at risk mental state (ARMS) for psychosis, a first psychotic episode (FEP) and controls were studied using fMRI while performing a working memory task. Activation in the superior temporal gyrus (STG) was assessed using Statistical Parametric Mapping (SPM), and its relationship to frontal activation was examined using Dynamic Causal Modelling (DCM).

Results - The STG was differentially engaged across the three groups. There was deactivation of this region during the task in controls, whereas FEP subjects showed activation and the response in ARMS subjects was intermediate relative to the two other groups. There were corresponding differences in the effective connectivity between the STG and the middle frontal gyrus across the three groups, with a negative coupling between these areas in controls, a positive coupling in the FEP group, and an intermediate value in the ARMS group.

Conclusions - A failure to deactivate the superior temporal lobe during tasks that engage prefrontal cortex is evident at the onset of schizophrenia and may reflect a disruption of fronto-temporal connectivity. Qualitatively similar alterations are evident in people with prodromal symptoms of the disorder.

Introduction

Structural and functional neuroimaging studies have described abnormalities in a wide range of different cortical and subcortical areas in schizophrenia (McGuire and Matsumoto, 2004). One of the areas that is robustly implicated is the superior temporal gyrus (STG), which is a consistent site of grey matter volume reductions in structural neuroimaging studies of schizophrenia (Wright et al, 2000; Honea et al, 2005). Functional neuroimaging studies in schizophrenia report abnormal activation of STG during performance of a range of cognitive tasks (Fletcher et al, 1996; Gur et al, 2007), and activity in this regions has been linked to the severity of auditory hallucinations (McGuire et al, 1995; Allen et al, 2007) and formal thought disorder (McGuire et al, 1998; Kircher et al, 2001).

Localized functional deficits do not appear to provide a satisfactory account of the range of clinical symptoms and cognitive impairments evident in schizophrenia, and it has been proposed that the disorder may be better understood in terms of faulty integration or connectivity between different brain areas (Friston and Frith, 1995; McGuire and Frith, 1996). In particular, it has been suggested that functional connectivity between the frontal and superior temporal cortex may be particularly dysfunctional in patients with schizophrenia (Frith et al, 1995; Fletcher et al, 1996; Lawrie et al, 2002; Wolf et al, 2007). However, there has been some inconsistency in the findings from studies of functional connectivity in schizophrenia, with two studies failing to find evidence of fronto-temporal dysconnectivity (Dye et al, 1999; Spence et al, 2000). An important factor in this variability of findings may be heterogeneity among the patient samples studied with respect to stage of illness and previous exposure to antipsychotic treatment (Fusar-Poli et al, 2008). The effect of these potentially confounding factors can be minimised by restricting studies to individuals in the early phase of psychosis, such that all the participants are at the same stage of illness and have received no or minimal previous treatment.

We adopted this approach in the present study, examining superior temporal lobe function and its functional connectivity in people who were experiencing prodromal symptoms but had not yet developed psychosis, and patients who just presented with a first episode of schizophrenia. As well as being medication-naïve, the prodromal group were of particular interest, as it allowed us to examine whether temporal lobe

dysfunction and abnormal functional connectivity are specifc to schizophrenia or are also evident in people at high risk of the disorder. The prodromal phase, termed the At Risk Mental State (ARMS) is associated with neurobiological alterations qualitatively similar to those observed in schizophrenia (Fusar-Poli et al, 2007), including cognitive deficits (Broome et al, 2007; Keefe et al, 2006; Wood et al, 2003), reductions in frontal and temporal grey matter volume (Pantelis et al, 2003; Borgwardt et al, 2007; Meisenzahl et al, 2008) and differential activation in frontal and temporal cortex during tasks of executive functions (Morey et al, 2005; Broome et al, 2009). Although all subjects with an ARMS experience 'prodromal' signs of psychosis, not all of them will subsequently develop a psychotic disorder. Large prospective studies following subjects with an ARMS have found that around 22-31% develop a psychotic disorder within the next year (Yung et al, 2007; Cannon et al, 2008). The search for biomarkers which might help predict which subjects will later develop psychosis is thus of great clinical importance.Functional integration has not previously been studied in the ARMS. However, altered fronto-parietal and fronto-cerebellar connectivity have been reported in the relatives of patients with schizophrenia, who are at increased genetic risk for the disorder, and can experience psychotic symptoms similar to those in the ARMS (Whalley et al, 2005).

The aim of the present study was to use functional MRI to assess temporal lobe function and its connectivity in the ARMS and first episode schizophrenia in the context of a working memory task (the N-back task). This paradigm was chosen for two reasons. First, performance on the N-back is robustly impaired in both the ARMS and in schizophrenia (Wood et al, 2003). Secondly, while functional imaging studies of the N-back in schizophrenia indicate that there may be reduced engagement of prefrontal cortex in patients relative to controls, several have reported that patients show relatively *increased* activation of the STG (Meyer-Lindenberg et al, 2001; Thermenos et al, 2005; Tan et al, 2006). In healthy volunteers, performance of visually presented working memory tasks has been shown to be associated with deactivation of the superior temporal cortex (Crottaz-Herbette et al, 2004), and relatively greater activation of this region in schizophrenia has been found to reflect a failure of superior temporal deactivation in patients (Menzies et al, 2007; Walter et al, 2007). In the present study we measured group differences in regional activation during a working memory task and then used Dynamic Causal Modelling (DCM; Friston et al, 2003; Mechelli et al, 2003b) to

examine effective connectivity within the network of regions it engaged. Effective connectivity refers to the influence that one neural system exerts over another and how this is affected by the experimental context.

Our first hypothesis was that the groups would show differential activation in the superior temporal cortex, with activation in the ARMS group intermediate to that in the FEP group and controls. The second hypothesis was that these differences in activation would be attributable to differences in effective connectivity between the STG and regions within frontal cortex.

Methods

Subjects

A total of 39 subjects participated. All were right-handed and native speakers of English. Subjects were excluded if there was a history of neurological disorder or if they met DSM-IV criteria for a substance misuse disorder. An ARMS group comprised 16 subjects who met PACE criteria (McGorry et al, 2003), recruited from OASIS, the local clinical service for people with an ARMS (Broome et al, 2005). The diagnosis was based on assessment by two experienced clinicians using the Comprehensive Assessment for the ARMS (CAARMS; Yung et al, 2003), and a consensus meeting with the clinical team. All these subjects were naïve to antipsychotic medication at the time of scanning. A first episode psychosis (FEP) group comprised 10 patients who had recently presented with a first episode of psychosis to LEO (http://www.slam.nhs.uk/services/), the local clinical service for first episode patients. All met ICD-10 criteria (WHO, 1992) for a schizophreniform psychosis at the time of scanning and OPCRIT criteria (McGuffin et al, 1991) for schizophrenia when assessed 12 months after presentation. Three of the first episode patients were unmedicated at the time of scanning. The other seven had been treated with either oral Risperidone or Quetiapine for a mean of 10 days (95% CI 4.7-16.3) at mean doses of 1.7 mg and 63.75 mg, respectively. A control group comprised 13 healthy volunteers recruited via advertisements in the local media. The three groups were matched for age and gender, and there were no significant differences between the groups in IQ and sociodemographic variables.

N-Back Task

Subjects were presented with a series of letters on a computer screen at 2 second intervals in 30 second blocks. During a baseline (0-back) condition, they were required to move a joystick to the left when the letter 'X' appeared. During 1-back and 2-back conditions, they were required to press a button on the joystick with their right index finger if the letter currently visible was the same as that presented 1 or 2 trials beforehand, respectively. The 3 conditions were presented in 10 alternating blocks matched for the number of target letters per block (i.e. 2 or 3), with each block preceded by an instruction slide. Reaction time and the accuracy of the responses were recorded on-line, and afterwards compared between the three groups using one way ANOVA.

Data Acquisition

Images were acquired in a 1.5 Tesla MRI scanner (Signa LX- GE system) at the Maudsley Hospital in London, using a TR of 2000ms and TE 40ms, 38 x 3mm slices, with an interslice gap of 0.3mm gap in 14 axial planes.

fMRI Data Analysis

All analyses were performed using SPM5 (http//www.fil.ion.ucl.ac.uk/spm) running in Matlab 7.0 (Mathworks Inc. Sherbon MA, USA). Preprocessing included realignment of all volumes in each subject using the first as reference, normalization to a standard MNI template using nonlinear-basis functions, and spatial smoothing with a 6mm full width at half maximum isotropic Gaussian kernel. An event related analysis was performed on the block-design acquired data. This type of analysis has shown to yield a more accurate model than an epoch-analysis (Mechelli et al, 2003a) and furthermore allowed us to model error trials (either missed targets or wrong non-targets) separately. Eight experimental conditions comprising the target and non-target events in each of the three task conditions (0-back, 1-back and 2-back) plus instructions and error trials were modeled by convolving their respective onset times with a canonical haemodynamic response function. A general linear model was used to calculate the parameter estimates for all brain voxels, and contrasts were created for each subject comparing non-target events while performing 1-back and 2-back tasks respectively versus 0-back condition (baseline). Non-target (rather than target) events were chosen as their greater number made them more appropriate for an event-related analysis, and because they were not associated with motor responses that might contribute to the BOLD response. A second level analysis was performed using the pooled 1 and 2-back contrasts to

identify areas activated in association with working memory consistently in the three groups, independent of mnemonic load (threshold of $p<0.05$, corrected with FWE with clusters >10, masked with contrasts of activated regions for each independent group at $p<0.001$). Likewise, differences in activation between the three groups were investigated using a statistical threshold of $p<0.05$, corrected with FWE and an extent threshold of 10 voxels. Within our a priori region of interest, the superior temporal cortex, group-related differences were identified using a statistical threshold of $p<0.001$ and an extent threshold of 10 voxels.

DCM analysis

The aim of DCM is to estimate and make inferences about the influence that one neural system exerts over another and how this is affected by the experimental context. In this study, DCM was used to find whether the differences found in the activation in the temporal lobe between the three groups were explained or modulated by abnormal connectivity from another brain region. No direct anatomical connections need to be assumed in DCM since it could happen that two remote areas are functionally connected through another relay region. Three distinct sets of connectivity parameters are estimated. A first set scale the direct and extrinsic influence of inputs on brain states in any particular region. These parameters are generally of little interest in the context of DCM but are the primary focus in classical analyses of regionally specific effects. A second set of parameters (which is the primary focus in this study) refers to the 'endogenous connections' that couple neuronal states in different regions, and allow one to estimate the rate of change of neuronal activity in one area induced by activity in another. As such, this characterization does not depend on the units of activity *per se*, but the 'speed' or rate of inter-regional influences. A third set of parameters or 'bilinear terms' reflects changes in the intrinsic coupling between regions that are induced by experimental manipulation and were not included in this study. The reader is referred to Friston et al (2003), and Mechelli et al (2003b), for further information about DCM.

In the present study, the DCM analysis was implemented in SPM5. As previously mentioned, we used a lower statistical threshold ($p<0.001$ uncorrected) to identify areas to be included in the DCM analysis in our a priori region of interest, namely the superior temporal cortex. Other regions entered in the analysis were identified according to two criteria: Firstly, regions activated in all three groups in association with the task.

Secondly, regions where there was differential activation between the FEP and control groups, with activation in the ARMS group at an intermediate level.

We limited the analysis to a single hemisphere to minimize the number of statistical comparisons and to avoid excessive computational demands. The left hemisphere was selected because the group differences in activation during this particular task were more marked than in the right (see results below). Individual subject maxima for each subject and for each region were identified allowing for inter-subject variation of the coordinates of +/- 6 units in each of the coronal, sagittal and axial planes. Their first principal component (eigenvariate) was extracted using a contrast for non-target events only. We built a model which all the regions identified (using the functional criteria above) were unidirectionally connected to the temporal lobe. External inputs (all non-targets events) were allowed to enter the model affecting each of the areas included, except the temporal lobe, in order to study the effect they had on the latter. Individual connectivity parameters between the different areas to the temporal lobe were compared between the three groups using ANOVA on ranks since it was not normally distributed. Finally, subjects within the ARMS group who later made a transition to psychosis were compared to those who did not in relation to its connectivity profile.

Results

Behavioural results

There were no significant group differences in number of missed targets in the three groups, with controls missing 1, ARMS 2.9 and FEP 3.1 ($p=0.19$). There were no significant group difference in number of misidentified non-targets either, with FEP making 5.6 errors, ARMS 1.6 and control 2.2 ($p=0.15$).

fMRI results

Areas activated in all three groups

During the N-back task (1-back and 2-back combined versus baseline) all three groups showed activation in a bilateral network of areas comprising the prefrontal, insular, cingulate, supplementary motor, posterior parietal and cerebellar cortex, plus the right caudate nucleus (Figure 1 and table 1).

(figure 1 and table 1 about here)

Areas differentially activated between groups

In the whole brain analysis, no significant differences between groups were detected at a threshold of $p<0.05$ (corrected for multiple comparisons across the whole brain). However, in the a priori region of interest, the superior temporal cortex, the FEP group showed greater activation than controls bilaterally, with differences more marked in the left hemisphere (Z-score 3.9, cluster size 126; $p<0.001$) than the right (Z-score 3.27, cluster size 13; $p<0.001$). This reflected activation of this region relative to baseline in the FEP group, in contrast to the deactivation seen in controls (Fig 2). The level of activation in the ARMS group was intermediate to that in the other two groups.

(figure 2 about here)

DCM results

We then used DCM to examine whether the group difference in superior temporal gyrus activation could be explained by an abnormal interaction between this region and frontal areas. The three frontal regions (the supplementary motor cortex, insula, and middle frontal gyrus) activated by the task in all three groups were selected to enter the DCM analysis, along with the posterior parietal cortex, which was also activated in all three groups and was included as an internal control (representing a non-frontal region engaged by the task) (see figure 1). Table 2 shows the coordinates of the 5 regions in the models and their Z-scores for each group for the [1-back + 2-back] > baseline contrast.

Table 2 about here.

A model connecting these four regions to superior temporal lobe was created for entering DCM analysis as shown in figure 3.

Figure 3 about here.

Individual coupling parameters between the four selected regions and the STG as modelled were compared using ANOVA on ranks as the data were found to be non-normally distributed. The connection between the middle frontal gyrus and the STG was

the only one that was significantly different between the three groups (H = 6.659, 2 degrees of freedom, P = 0.036).

Post-hoc analysis corrected for multiple comparisons using a Bonferroni based method showed a significant difference between FEP and controls, with FEP having a positive coupling between the middle frontal gyrus and superior temporal regions (median 0.00830; 25% 0.00670, 75% 0.0195) while controls showed a negative coupling (median -0.0076; 25% -0.0157, 75% 0.0078). In the ARMS group, there was an intermediate coupling between that in the other two groups (median 0.00180; 25% -0.00380, 75% 0.0160). The coupling parameters in each subject are displayed in the scatter plot in figure 4.

Figure 4 about here.

Clinical correlates

During the 24 month follow-up period 2 of the ARMS group made a transition to a psychotic disorder. Their coupling parameters were 4th and 16th (of n=16) when ranked from highest to lowest within the cohort (subjects highlighted in figure 4 with black).

Discussion

The aims of the present study were to investigate (i) whether there was differential activation of superior temporal cortex in ARMS, FEP and control subjects during a working memory task analysed with an event related analysis, and if so, (ii) whether this could be explained by the altered connectivity between this region and frontal cortex. We found that the FEP group and to a lesser extent the ARMS group expressed increased activation in the superior temporal cortex relative to the control group in the working memory task. We then constructed a DCM model comprising areas that were consistently activated in all groups (prefrontal, insula, supplementary motor areas and posterior parietal). The three selected frontal regions have been previously reported as sites of abnormalities in structural and functional neuroimaging studies of schizophrenia (supplementary motor area – Ortuño et al, 2005; insula – O'Daly et al, 2007; prefrontal cortex – Fu et al, 2005), raising the possibility that their connections to STG could be altered in FEP and ARMS. Examination of the individual connections of each area with the STG revealed a differential coupling between middle frontal gyrus and STG between

the three groups, with controls displaying a negative coupling, FEP a positive coupling, and the coupling in the ARMS intermediate and close to neutral.

This study provides further evidence for a perturbation of fronto-temporal connectivity in schizophrenia and the first evidence that alterations in connectivity may also be a feature, albeit to a lesser degree, in non-psychotic people experiencing prodromal symptoms of the disorder. Most previous evidence of fronto-temporal dysconnectivity in schizophrenia has been based on studies of chronically ill patients. As a result it was not possible to know whether the findings were related to effects of several years of illness or its treatment with antipsychotic medication, both of which are associated with functional and volumetric changes in the brain (Chakos et al, 1994; Cahn et al, 2002; Dazzan et al, 2005). Here we were able to minimise these potentially effects by studying patients who had only recently developed psychosis and had relatively little previous exposure to antipsychotic medication. Our data indicate that an alteration in fronto-temporal coupling is already present in the early stages of schizophrenia, and thus unlikely to be attributable to effects of illness progression or treatment subsequent to the first episode of psychosis, as it could apply to data from patients with chronic psychosis. However, there still could be a progressive deterioration of fronto-temporal coupling in the period between the ARMS and the transition to frank psychosis, as there is evidence that there are longitudinal volumetric changes in cortical grey matter at this stage (Pantelis et al, 2003; Borgwardt et al, 2008). To address this issue, the present study would need to be repeated in a larger sample with a larger number of transitions. We cannot exclude the possibility that the small amount of antipsychotic medication given to some participants in the FEP group may have influenced the results. Previous studies have shown that BOLD signal (Jones et al, 2004; Snitz et al, 2005) as well as functional connectivity (Stephan et al, 2001) are affected by atypical antipsychotics. The small number of subjects taking antipsychotic medication did not allow us to test for these effects statistically; however, the fact that qualitatively similar abnormalities were evident in the medication naïve ARMS group indicates that the contribution of antipsychotic medication to our results was not significant. Our findings of altered connectivity in the ARMS group are consistent with data from a recent study of another group at increased risk of psychosis, the relatives of patients with schizophrenia, although that study involved a different task that engaged different set of regions, and it examined inter-regional correlations rather than effective connectivity (Whalley et al, 2005).

Abnormal frontal lobe function has been consistently implicated in schizophrenia. As we found that the abnormal temporal activation was related to a reversed coupling with a frontal region, the temporal dysfunction could be interpreted as an epiphenomenon of a macro-circuit alteration stemming from abnormal frontal activity. This mechanism was originally suggested by Friston and Frith (Friston and Frith, 1995), who explained hyperactivation of the temporal lobe in schizophrenia during a verbal fluency task as a 'second order effect' of perturbed frontal lobe function.

The presence of qualitatively similar changes in the ARMS to those in first episode schizophrenia suggests that this may be a correlate of the increased vulnerability of this group to the disorder. There was some heterogeneity in the strength of fronto-temporal coupling population within the ARMS sample: some subjects had positive coupling parameters similar to those in FEP patients, while others displayed a negative coupling, as in most of the controls (figure 4). However the subjects within the ARMS group who later made a transition to psychosis did not appear to be outliers and their coupling parameters were not as positive as the FEP sample (highlighted in figure 4), although the small number of subjects involved precludes concluding anything from this observation about the predictive value of these changes. Whether this coupling parameter could inform prediction of subsequent conversion to psychosis will require investigation in samples large enough to yield a larger subgroup of subjects who make a transition.

There are a number of strengths to the present investigation. First, we used an event-related analysis that modelled errors independently. Controlling for performance may be critical to identifying the involvement of the superior temporal gyrus in visually presented working memory tasks; in one study the failure to deactivate the STG in schizophrenia was only evident when patients and controls were adequately matched according to response rates (Thermenos 05). Second, we chose a hypothesis-driven approach using DCM to look at the effective connectivity, constraining the initial areas studied that could affect STG on the basis of the results found in the classical fMRI data instead of using an analysis of functional connectivity which is based on simple correlations.

As explained in the methods, we restricted our analysis to the left hemisphere. Although the right hemisphere showed similar activation during the task, we cannot necessarily conclude that similar connectivity alterations would be found. Finally, we note that the difference in effective connectivity between prefrontal and superior temporal cortex was detected without performing a correction for multiple comparisons to account for the fact that a total of 4 pathways were investigated within our network of interest. However, a typical correction for multiple independent comparisons, such as Bonferroni, would have been inappropriate (i.e. too conservative) because the four pathways investigated were not independent but part of the same functional network. Further studies are required to replicate our finding in independent samples of individuals with FEP and ARMS.

Conclusions

In conclusion, the present investigation suggests that the failure to deactivate the superior temporal cortex previously reported in patients with chronic schizophrenia is also evident at the onset of psychosis and, to a lesser extent, in subjects at high risk of the disorder. Furthermore, the present investigation provides support to the idea that this dysfunction can be explained in terms of fronto-temporal dysconnectivity.

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Legends of figures

Figure1. Areas activated when subjects from the three groups were perfoming the working memory tasks. Regions showed correspond to the combined 1 and 2-back conditions against 0-back condition, with a threshold of $p<0.05$, corrected with FWE with clusters >10 and masked with contrasts of activated regions for each independent group at $p<0.001$. Coordinates and Z-scores are reported in table 1.

Figure 2. Comparison of FEP and Controls when performing the working memory task. Only areas significant at $p<0.001$ uncorrected and with cluster size>10 are shown. Bold signal from the highlighted area in the STG is shown in the lower graph. The two columns in each group represent the 1- and 2-back conditions. Notice that in both conditions the FEP group showed activation of the STG, in contrast to the deactivation evident in controls. The ARMS group showed an intermediate pattern of activation in this region.

Figure 3. Model connecting selected regions to superior temporal gyrus (STG). Note that the directions of the connections are unidirectional to STG. SMA= Supplementary Motor Area; MFG= middle frontal gyrus; INS= insula; PAR= posterior parietal.

Figure 4. Scatter plot of coupling parameters (rate of change in activation per unit of time) for each subject in the three groups. Coupling between prefrontal and superior temporal cortex was positive in the FEP group, negative in controls and around neutral in the ARMS group. Highlighted with black diamonds are the two subjects in the ARMS group who later made the transition to psychosis (see text).

Table 1

Region	***Cluster size***	***Co-ordinates***	***Z-score***
Right Middle Frontal Gyrus	1568	32 0 56	Inf
		46 4 38	Inf
		40 32 40	7.25
	45	38 50 28	6.8
Left Parietal Lobe	940	-36 -50 50	Inf
		-14 -72 56	7.35
Right Parietal Lobe	1313	38 -42 44	Inf
		28 -64 58	7.21
		36 -56 54	7.21
Left Middle Frontal Gyrus	1734	-26 0 56	Inf
		-46 26 38	7.75
		-40 2 34	7.57
	1568	-44 44 26	5.73
Supplementary Motor Area/	324	0 14 52	7.33
Cingulate Gyrus		8 20 42	6.77
		6 4 56	6.06
Left Insula	380	-34 18 2	7.32
Right Insula	308	38 24 -4	7.1
Left Cerebellum	18	-32 -60 -32	6.6
Right Caudate	125	16 -4 20	6.53
Right Cerebellum	16	30 -66 -30	6.4
Left Superior Frontal Gyrus	42	-36 56 14	6.07
	89	-36 46 30	6.01

Table 2

AREA *(all in left hemisphere)*	*CO-ORDINATES*			*Z-SCORES* *([1-back + 2-back]> 0-back)*		
	x	y	z	Controls	ARMS	FEP
Superior Temporal Gyrus	-44	-20	8	-2.87	0.21	2.81
Supplementary Motor Area	0	14	52	6.17	4.14	4.10
Middle Frontal Gyrus	-46	26	38	5.09	5.98	4.17
Insula	-34	18	2	4.54	4.89	4.82
Posterior Parietal Cortex	-36	-50	50	7.09	5.16	4.50

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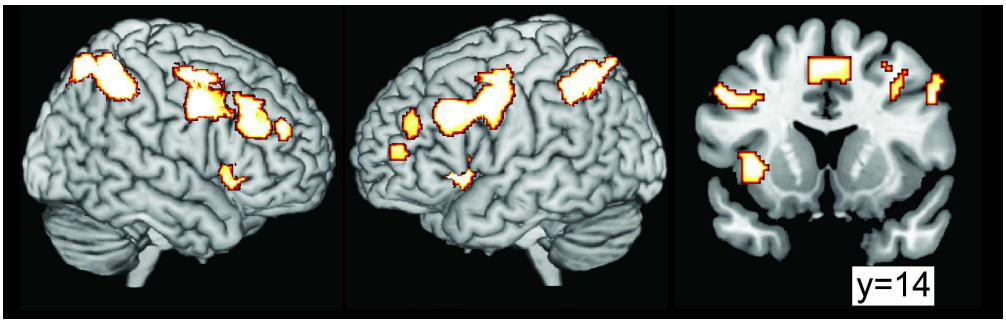

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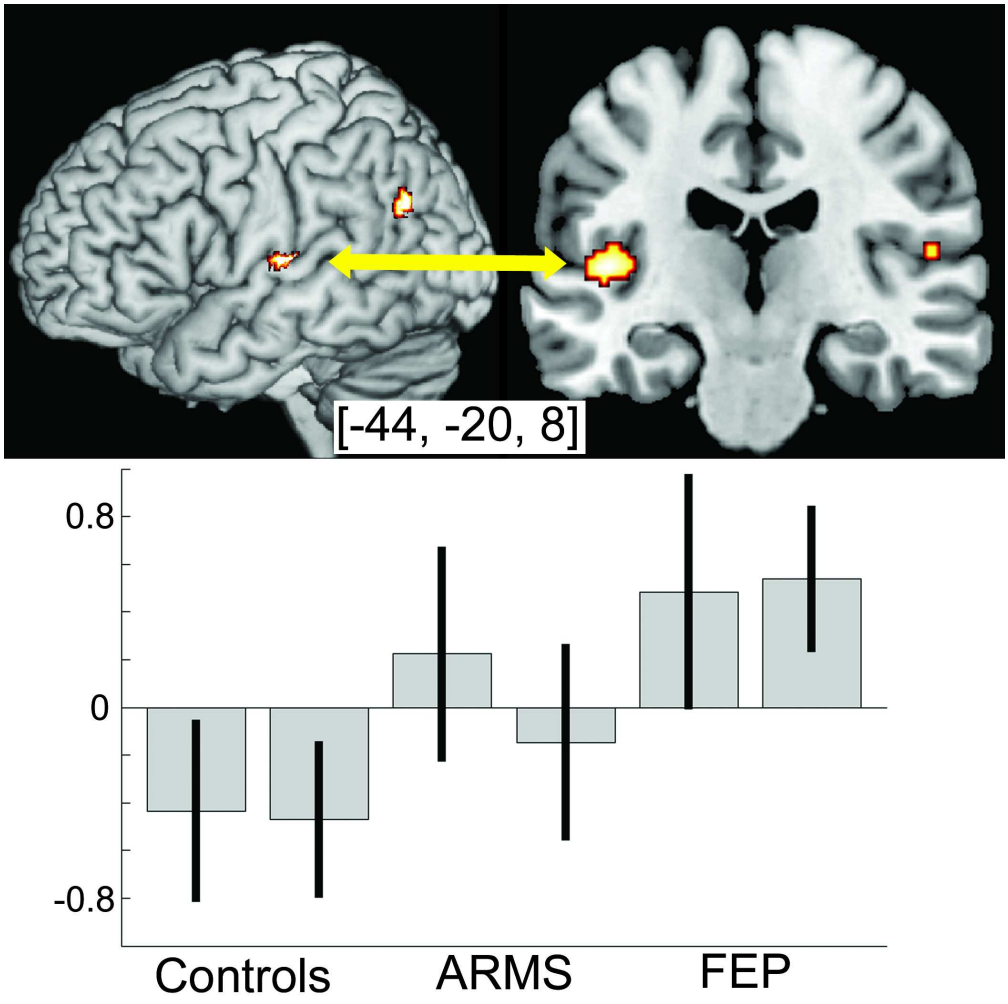

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88x88mm (600 x 600 DPI)

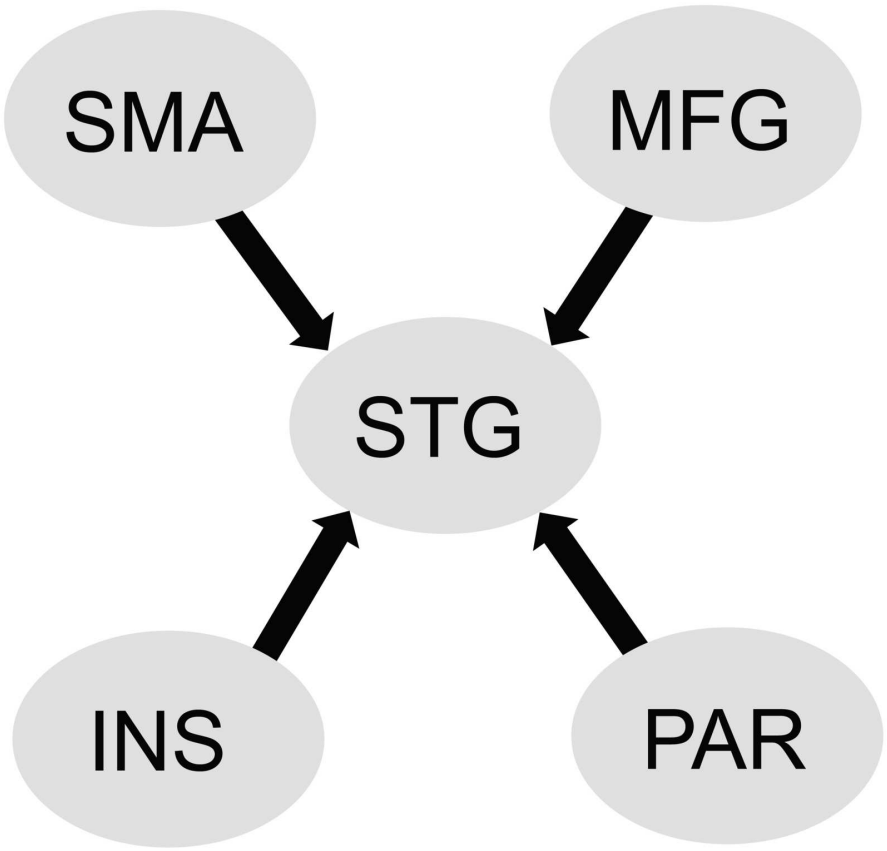

Figure 3. Model connecting selected regions to superior temporal gyrus (STG). Note that the directions of the connections are unidirectional to STG. SMA= Supplementary Motor Area; MFG= middle frontal gyrus; INS= insula; PAR= posterior parietal.
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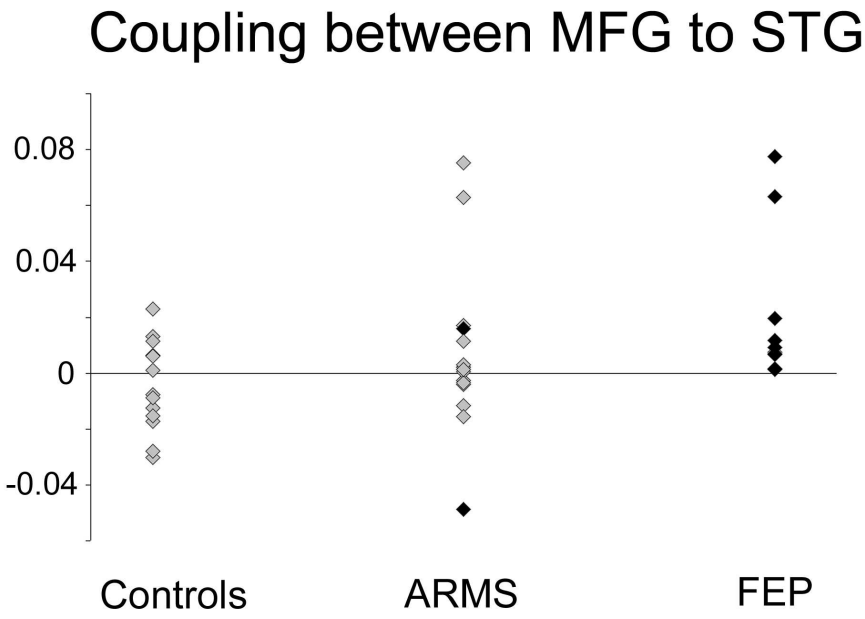

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88x62mm (600 x 600 DPI)