Increased Inferior Frontal Activation During Word Generation: A Marker of Genetic Risk for Schizophrenia but not Bipolar Disorder?

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Abstract: During verbal-fluency tasks, impairments in performance and functional abnormalities in the inferior frontal cortex have been observed in both schizophrenia patients and their unaffected relatives. We sought to examine whether such functional abnormalities are a specific marker of genetic vulnerability to schizophrenia. We studied a sample of 132 subjects, comprising 39 patients with schizophrenia, 10 unaffected monozygotic (MZ) cotwins of schizophrenia probands, 28 patients with bipolar disorder, 7 unaffected MZ cotwins of bipolar disorder probands and 48 healthy controls. Blood oxygen level-dependent response was measured using functional magnetic resonance imaging during the performance of an overt verbal-fluency task with two levels of task difficulty, in a cytoarchitectonic region of interest encompassing Brodmann areas 44 and 45 bilaterally. Patients with schizophrenia and the unaffected MZ cotwins of schizophrenia probands showed increased activation in the inferior frontal cortex relative to healthy controls and bipolar patients. Increased engagement of the inferior frontal cortex during verbal-fluency may thus be a marker of genetic vulnerability to schizophrenia. *Hum Brain Mapp* 30:3287–3298, 2009. © 2009 Wiley-Liss, Inc.

Key words: schizophrenia; bipolar disorder; verbal fluency; twin study; functional magnetic resonance imaging

INTRODUCTION

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Phonological, or letter, verbal fluency is a classic measure of executive function and language processing, which involves subjects generating a word beginning with a given letter [Benton et al., 1994]. Patients with schizophrenia produce, on average, fewer words than healthy subjects in letter fluency tasks [Heinrichs and Zakzanis, 1998]. This deficit has also been verified in the unaffected relatives of schizophrenia subjects [Snitz et al., 2006; Szoke et al., 2005], thus constituting a potential biomarker of genetic liability, or endophenotype [Bearden et al., 2007; Gottesman and Gould, 2003], for schizophrenia. Although patients with bipolar disorder also show reduced performance during verbal fluency relative to controls, their

impairment is significantly less pronounced than that of schizophrenia subjects [Krabbendam et al., 2005], and it may not extend to their unaffected relatives [Arts et al., 2007; Bora et al., 2008], suggesting specificity in the link between verbal fluency impairment and vulnerability to schizophrenia.

In healthy subjects, verbal fluency reliably engages left Brodmann areas (BA) 44 and 45, and also, to a lesser extent, their right hemisphere homologues [Costafreda et al., 2009]. Brodmann areas 44 and 45 in the left hemisphere are often identified with the classical area of Broca, linked to language comprehension and production by neuropsychological lesion data and functional neuroimaging evidence [Baldo et al., 2006; Costafreda et al., 2006; Damasio, 1992; Fiez and Petersen, 1998]. Broca's counterpart in the right hemisphere is often active during language tasks [Gernsbacher and Kaschak, 2003], although its functional role during word production is more disputed [Price and Crinion, 2005]. There is also neuropsychological evidence linking inferior frontal cortex integrity with letter fluency performance [Stuss et al., 1998, 2003], suggesting that the performance deficits observed in schizophrenia may be associated to abnormal function in this region.

Consistent with this link, functional neuroimaging studies have identified significant differences between schizophrenia subjects and healthy controls in inferior frontal cortex during verbal fluency [Boksman et al., 2005; Curtis et al., 1998; Fitzgerald et al., 2007; Fu et al., 2005; Jones et al., 2004; Razafimandimby et al., 2007; Schaufelberger et al., 2005; Sommer et al., 2001b, 2003; Weiss et al., 2006]. Such functional abnormalities also extend to unaffected relatives of schizophrenia subjects [Sommer et al., 2004b; Spence et al., 2000; Whyte et al., 2006]. Moreover, gray matter density in Broca's area and its right hemisphere homolog has been shown to be highly influenced by genetic factors [Glahn et al., 2007], further supporting a role for inferior frontal cortex function as an endophenotype for schizophrenia liability.

Callicott et al. [2003a,b] have observed that schizophrenia subjects and their unaffected siblings require higher levels of activation in dorsolateral prefrontal cortex than healthy controls, to achieve comparable performance in a working memory task. Using a semantic verbal-fluency task, where participants are required to produce words based on their meaning (e.g., animals), Ragland et al. [2008] also reported increased activation in left prefrontal areas in schizophrenia subjects relative to controls, in the absence of performance differences. In the present work, we hypothesize an analogous link between inferior frontal cortex activation and verbal fluency whereby, after accounting for verbal-fluency performance, schizophrenia subjects and their unaffected monozygotic (MZ) twins would display an excess of activation in inferior frontal cortex relative to the healthy and bipolar control groups.

We employed modeling of fMRI measurements of twin and singleton data to determine whether functional abnormalities in inferior frontal cortex during verbal fluency

could be considered an endophenotype for schizophrenia. To assess the specificity of potential findings to schizophrenia, we also included a sample of healthy subjects, and of subjects with bipolar disorder. By using an overt letter fluency paradigm we were able to directly measure task performance online. Because of the role of Broca's area in language production, and the evidence regarding abnormal activation in this area and its right hemisphere homolog in schizophrenia, we examined activation in a cytoarchitectonic region of frontal cortex defined by Brodmann areas 44 and 45 [Amunts et al., 1999].

METHODS

Participants

To test the hypothesis on inferior frontal cortex function, we obtained retrospective data from four pre-existing studies conducted at the Institute of Psychiatry, King's College London, United Kingdom, one of which recruited only singleton subjects, whereas the others recruited singleton and twin subjects. The same standardized verbal fluency neuroimaging protocol was included in all four studies as a test of executive function in pathological populations. The task was originally designed for the Alien Voices study, which included singleton subjects with schizophrenia and healthy controls [Fu et al., 2002, 2005]. The Maudsley Family study is an ongoing project recruiting families with a history of schizophrenia or bipolar disorder [McDonald et al., 2004]. The Maudsley Schizophrenia Twin study and Bipolar Twin study are recruiting twin pairs concordant and discordant for schizophrenia and bipolar disorder, respectively, along with healthy control MZ twins [Toulopoulou et al., 2007]. The subjects included in the present paper were recruited from 2002 to 2007, except for the Alien Voices study, which completed its recruitment in 2004. All projects were approved by the Ethics Research Committee at the Institute of Psychiatry, London, England. All participants provided written, informed consent.

From a full sample of 244 subjects, we included English-speaking, medically healthy volunteers with the following exclusion criteria: age below 18 or above 65 years, history of a psychiatric or neurological disorder or current substance abuse or dependence (or comorbidity in patient groups). After visual inspection of the fMRI time-series, data from 17 subjects (5 bipolar, 9 schizophrenia and 3 healthy controls) had to be discarded because of acquisition artifacts or incomplete coverage of inferior frontal area.

The final sample consisted of 132 participants: 39 patients with schizophrenia, 10 unaffected MZ twins of patients with schizophrenia, 28 bipolar disorder patients, 7 unaffected MZ twins of patients with bipolar disorder and 48 healthy controls (Table I). In total, 41 MZ twin pairs (82 subjects), as determined by genetic analysis, and 50 singletons were included in the sample. Among

TABLE I. Subjects' characteristics and group task performance

	Sz, <i>n</i> = 39	UT Sz, <i>n</i> = 10	Bip, <i>n</i> = 28	UT Bip, <i>n</i> = 7	Controls, <i>n</i> = 48	Analysis		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	df	<i>F</i>	<i>P</i>
Age (years)	35.6 (10.5)	28.2 (8.9)	40.0 (12.4)	39.4 (15.8)	37.4 (9.8)	4,127	2.43	0.051
IQ	101.1 (14.1)	103.0 (12.8)	106.5 (13.4)	107.3 (9.1)	106.5 (13.0)	4,127	1.17	0.325
Education (years)	14.2 (2.5)	14.1 (2.5)	14.7 (3.2)	16.4 (3.7)	14.5 (2.8)	4,127	0.98	0.422
Gender, Men:women	30:9	8:2	12:16	1:6	25:23	4	16.48	0.002 ^a
Ethnicity, caucasian:other	33:6	10:0	26:2	5:2	45:3	4	6.13	0.189 ^a
Handedness, right:left	37:2	8:2	26:2	7:0	46:2	4	4.28	0.369 ^a
Disease duration (years)	11.7 (7.8)		16.6 (12.4)			1,40	1.91	0.175
Number of twins:singletons	24:15	10:0	13:15	7:0	28:20	2	2.050	0.358 ^a
Word output, easy condition	29.6 (4.4)	29.3 (3.5)	30.2 (4.9)	31.3 (3.9)	30.8 (3.4)	4,127	0.7	0.596
Word output, difficult condition	26.4 (4.4)	25.0 (3.4)	28.1 (5.4)	27.4 (6.0)	27.9 (5.4)	4,127	1.17	0.328

^aFor ethnicity, number of twins, gender and handedness, the *P* value corresponds to a chi-square test for independence between each variable and diagnostic group. For number of twins, the test compares the proportions between the schizophrenia, bipolar and healthy control samples only.

For the rest of the variables, the *P* value corresponds to an *F* test with df(df1 = number of groups – 1, df2 = number of subjects – number of groups).

Sz, Schizophrenic subjects; UT Sz, Unaffected twins of schizophrenia subjects; Bip, Bipolar subjects; UT Bip, Unaffected twins of bipolar subjects; controls, healthy controls; df, degrees of freedom.

participants with schizophrenia, there were 7 MZ twin pairs where both siblings were affected and the bipolar disorder group included three MZ twin pairs concordant for the disorder. Among control subjects, there were 14 MZ twin pairs where both siblings had no psychiatric disorder.

Demographic and clinical characteristics of the sample are summarized in Table I. Handedness was estimated psychometrically using the Annett scale [Annett, 1970]. Verbal IQ was measured psychometrically using the Wechsler Abbreviated Scale of Intelligence [WASI, Wechsler, 1999] in the studies that recruited bipolar subjects and healthy controls, whereas premorbid IQ was estimated using the National Adult Reading Test [NART; Nelson, 1983] in the studies involving schizophrenia participants. In a large sample of schizophrenia and bipolar patients, relatives of these individuals and healthy controls [McIntosh et al., 2005], NART scores were essentially the same as verbal WASI scores for bipolar disorder patients, unaffected relatives and controls, and only substantially differed for schizophrenia participants, as would be expected from measures of premorbid (NART) and present (WASI) IQ. Clinical and neuropsychological characteristics of the sample are summarized in Table I. There were no significant differences across groups with respect to IQ, years of education, ethnic origin, handedness, disease duration and number of twins in each sample. The groups differed in gender distribution (*P* = 0.002), with a higher proportion of males in the schizophrenia sample. The test for age differences across groups approached significance (*P* = 0.051), largely driven by the younger age of the unaffected twins of schizophrenia subjects.

In the schizophrenia group, 35 patients were on a drug therapy regime at the time of scanning. Of these, 30 indi-

viduals were taking atypical antipsychotics and 5 conventional antipsychotics. The mean chlorpromazine equivalent daily dose was 638.6 (SD = 435.2) mg/day. Five participants with schizophrenia additionally received coadjuvant medication, which were SSRI antidepressants in two cases and a mood stabilizer in three cases. Symptomatology was rated with the Scale for the Assessment of Positive Symptoms [SAPS; Andreasen, 1984] and the Scale for the Assessment of Negative Symptoms [SANS; Andreasen, 1983], with mean ratings of 6.9 (SD = 7.9) positive scale and 7.8 (SD = 4.6) negative scale. All bipolar disorder patients suffered from type I disorder, and 22 of them were on medication. Of these, 20 patients were taking regular doses of a mood stabilizer drug, which was lithium in 10 cases (mean dosage of 860.0 mg/day; SD = 211.9 mg/day); 5 subjects were taking regular doses of antipsychotic medication (2 as monotherapy) and 5 subjects were on antidepressants. None of the bipolar disorder participants currently fulfilled criteria for a major depressive or manic episode, and none had active psychotic symptoms. Clinical status for 13 bipolar patients from the Maudsley Family study was measured by self-report: mean of 7.86 (SD = 7.5) in the Beck Depression Inventory [Beck et al., 1989] and mean of 3.4 (SD = 2.3) in the Altman Self-Rating Mania Scale [Altman et al., 1997]; and for 15 patients from the Maudsley Bipolar Twin study, the clinical ratings were: mean 6.6 (SD = 6.2) in the Hamilton Depression Rating Scale [Hamilton, 1967] and mean 1.33 (SD = 3.42) in the Young Mania Rating Scale [Young et al., 1978].

Overt Verbal-Fluency Task

The experimental condition was a phonological letter fluency task [Lezak, 1995] with two levels of difficulty

[Fu et al., 2002]. Subjects were instructed to overtly generate a word in response to a visually presented letter shown at a rate of one every 4 sec, while avoiding proper names, repetitions and grammatical variations of previous words [Lezak, 1995]. If subjects were unable to think of a response, they were asked to say “pass”. The difficulty of the condition depended on which set of letters was presented. The letters were categorized as “easy” (set TLBRS or TCBPS) and “difficult” (set OANEG or IFNEG) according to the mean number of erroneous responses they generated in a previous study [Fu et al., 2002]. There were seven presentations of each letter (28 s experimental block), followed by the control condition which was repetition of the word “rest” presented at the same rate (28 s control block). The “easy” and “difficult” conditions were presented in a randomized order between subjects. Verbal responses during scanning were recorded and correct word output did not significantly differ between groups (Table I).

fMRI Data Acquisition

All scanning was done following the same procedure on the same acquisition system [Fu et al., 2002, 2005]. Seventy-four T2*-weighted gradient-echo single-shot echo-planar volumes were acquired on a 1.5-T neuro-optimized GE LX System (General Electric, Milwaukee) at the Maudsley Hospital, SLAM NHS Trust. Each volume consisted of 12 noncontiguous axial planes (7 mm thickness, slice skip 1 mm, TE = 40 msec, flip angle = 90 degrees) parallel to the anterior commissure–posterior commissure line. Images were collected using a “clustered” sequence, in which data acquisition took only the first 1,100 msec of each TR, to allow subjects to make overt responses in relative silence. A letter was presented (remaining visible for 750 msec, height: 7 cm, subtending a 0.4 degrees field-of-view) immediately after each acquisition, and a single overt verbal response was made during the remaining silent portion (duration = 2,900 msec) of each repetition (TR = 4,000 msec).

fMRI Data Analysis

The fMRI data were realigned to remove residual motion effects, transformed into standard MNI space, and smoothed in space with an isotropic Gaussian filter (FWHM = 8 mm), using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). A high-pass filter (cutoff 128 sec.) was employed to remove low-frequency drifts. Subject-level model estimation was also performed in SPM2 using a standard convolution model and assuming an autoregressive correlation of depth 1 (AR1). Motion parameters were included in the analysis as covariates of no interest. We, thus, obtained two effect size maps per subject, one for each of the conditions (easy and difficult) for the contrast between word production and word repetition. These maps were in units of percent change of the blood oxygenation level dependent (BOLD) response rela-

tive to baseline. Using the SPM Anatomy Toolbox [Eickhoff et al., 2005], a mask image was obtained containing the voxels in MNI space belonging to the cytoarchitecturally defined BA areas 44 and 45 bilaterally with a probability of at least 50% [Amunts et al., 1999] (see Fig. 1). Using this cytoarchitectonic template provided a valid and probabilistically defined ROI, easily reproducible in other imaging datasets.

This mask was applied to the subject-level effect size images to extract data from selected voxels for the between-subject modeling stage. In this second stage, the analysis procedure had to cope with a complex within and between-subject correlational structure. The sources of correlation were two repeated measures for each subject (easy and difficult task runs), and the presence of twin sets as between-subject clustering factors. Ignoring these clustering effects in the analysis may lead to invalid and, in general, overconfident results [Pinheiro and Bates, 2000].

Conventional higher-level (multisubject) fMRI methods of analysis may still cope with these complex designs by splitting the observations in levels to be fitted separately according to these clustering variables [Mumford and Nichols, 2006]. However, given that adjustment for covariate effects at the intrasubject (number of valid words produced for each run) and subject level (age and gender) was required, and that subject clusters were limited to two individuals (twin sets), such a split-level approach would not have led to an identifiable model. In other words, not all model parameters could have been estimated with the available data. We, therefore, employed an “all-in-one” procedure, where the full dataset is analyzed in a single step that takes into account its hierarchical structure. In such an approach, the estimates from clustering units with few observations may “borrow strength” and be made more precise from what can be estimated from other clustering units in the model [Gelman et al., 2004].

A spatial Bayesian hierarchical model, suitable for such integrated estimation, has been recently described for fMRI data [Bowman et al., 2008]. We employed this method with modifications to fit a general multilevel linear model to our data whereas treating subjects and twin pairs as random effects. Full details on the modified model and its implementation are found in Appendix. Briefly, we assumed that voxel-specific effect size measurements varied about an area-specific mean, determined by the sum of a population-level mean parameter and a random effect component. The area-specific population-level mean was itself a linear function of fixed and random effects. Diagnostic group, the variable of interest in the analysis, was included as a fixed effect. Also present in the model were the following covariates: gender, age, task difficulty and output (i.e., the number of valid responses). Continuous variables were centered to their mean value before model estimation. Clustering variables were modeled through the addition of two area-level random effect terms, for twin and individual-specific effects assumed independent of each other and of the area-specific residual error term. Each random effect term was

Figure 1.

Region of interest investigated in the present study, containing the voxels in MNI space with a high probability ($\geq 50\%$) belonging to the cytoarchitecturally defined Brodmann areas 44 and 45 bilaterally. Left BA 44 is depicted in orange, left BA 45 in brown, right BA 44 in red and right BA 45 in white. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

also assumed to follow a multivariate normal distribution, with functional correlations across areas captured through its covariance matrix.

In this approach, the joint posterior distribution models the spatial correlation within and between areas, by assuming a hierarchical spatial dependency. The voxels within an area are considered identically and independently distributed, given their area populational mean. These area-specific mean are then given an unstructured variance–covariance matrix, to be estimated from the data. An advantage of this method is that it is based on anatomical or cytoarchitectural boundaries, which we know, are likely to separate functional entities [Eickhoff et al., 2006]. The reader is referred to the introduction of Bowman et al. [2008] for a detailed survey of the topic and justification of this approach.

In practical terms, an important consequence of this modeling approach is to enforce an area-specific smoothing of the voxel-level parameters, whereby voxel-level estimates are pulled towards their area mean. In other words, voxel-level estimates that look implausible (too large or small) in the context of their spatial neighborhood are neutralized. The net effect of this smoothing is an area-specific counterpart to the usual multiplicity correction [Greenland, 2006]. Further adjustments of the computed credible intervals (CI, the Bayesian analog of the confidence interval) through a multiplicity correction strategy would be inappropriate [Bowman et al., 2008]. Another consequence is that the method is most powerful to detect area-level activations, and may fail to detect small subareas of activa-

tion or large, but weak, large-scale activations encompassing several areas. This is a consequence of the matched filter theorem, and it is shared with other methods of higher-level analysis.

Using Markov Chain Monte-Carlo methods [Gelman et al., 2004], we obtained random samples from the joint posterior probability distribution of the model parameters. From these samples, we computed the voxel-wise sample mean as a best estimate of each parameter and a 95% credible interval to reflect its variability. Similar to Bowman et al. [2008], a thresholded posterior probability map [Friston and Penny, 2003] was obtained for each fixed effect parameter by plotting the voxel-wise mean of the marginal posterior distribution of the parameter, but only if their 95% CI did not include zero, that is, only for voxels with sufficient evidence that a true effect existed. We also provide the mean estimates and credible interval limits for the cluster maxima of the fixed effects maps.

RESULTS

During verbal fluency, healthy controls showed increased hemodynamic response in the left inferior frontal cortex during word generation relative to word repetition (Fig. 2a, Table II). Subjects with schizophrenia displayed an additional increase in activation in inferior frontal cortex bilaterally relative to healthy controls (Fig. 2b), when performing the verbal-fluency task, after controlling for task performance. The maxima of increased activation were located bilaterally in BA44 and in left

Figure 2.

Areas of significant changes in fMRI response for (a) healthy controls, word production versus word repetition, (b) contrast between schizophrenia participants versus healthy controls, (c) versus bipolar subjects, (d) unaffected twins of schizophrenia subjects relative to healthy controls and (e) versus bipolar disorder

patients. The maps depict the effect sizes Beta in units of percent change of fMRI response, thresholded at $P < 0.05$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

BA45 (Table II). Schizophrenia patients demonstrated increased bilateral activation relative to bipolar disorder patients bilaterally as well (Fig. 2c). Unaffected MZ co-twins of schizophrenia probands also showed a statistically significant increase in activation relative to healthy controls and bipolar disorder subjects, limited to the right hemisphere (Fig. 2d,e). Activation maps for bipolar disorder patients and their unaffected MZ twins did not show significant differences from healthy controls maps. For completeness, we also present the effect of the covariates included in the analysis (age, gender, task difficulty and word output) as Supporting Information.

DISCUSSION

We found increased engagement of the inferior frontal cortex while performing a verbal-fluency task in schizo-

phrenia patients and unaffected identical twins of schizophrenia probands relative to healthy controls and bipolar disorder subject. These findings were independent of the number of correct words produced by the subject. In other words, at any given task-performance level, participants with schizophrenia and their unaffected MZ twins had a more intense fMRI response in the inferior frontal cortex than healthy volunteers and bipolar disorder subjects. The detection of this exaggerated response in the unaffected identical twins of schizophrenia probands as well suggests that increased inferior frontal cortex activation may be linked to the genetically mediated risk of schizophrenia, rather than simply to the disorder itself.

Callicott et al. [2003a,b] have noted a similar candidate endophenotype in the same population, using a working memory task. They observed that both schizophrenia subjects [Callicott et al., 2003b] and their unaffected siblings

TABLE II. Activation maxima

	Left hemisphere					Right hemisphere				
	<i>x</i>	<i>y</i>	<i>z</i>	Beta	95% CI	<i>x</i>	<i>y</i>	<i>z</i>	Beta	95% CI
Controls										
BA44	-58	16	8	0.65	[0.49;0.81]					
Sz > Controls										
BA44	-54	14	0	0.43	[0.27;0.59]	56	14	0	0.59	[0.43;0.75]
BA45	-56	22	16	0.39	[0.24;0.56]					
Sz > Bipolar										
BA45	-56	32	8	0.32	[0.16;0.48]	56	28	16	0.75	[0.59;0.91]
Utsz > Controls										
BA45						56	22	8	0.39	[0.18;0.64]
Utsz > Bipolar										
BA45						56	28	8	0.48	[0.26;0.70]

The effects sizes Beta are in units of percent change of the blood oxygenation level dependent (BOLD) response relative to baseline. Sz, schizophrenic subjects; UT Sz, unaffected twins of schizophrenic subjects; CI, credible interval.

[Callicott et al., 2003a] required higher levels of activation in dorsolateral prefrontal cortex than healthy controls, to achieve a normal performance. They used the term “functional inefficiency” to describe this phenomenon, as this increase in fMRI response did not produce greater performance accuracy. Our findings can be interpreted in a similar fashion.

Our results are also compatible with previous functional brain imaging language studies in schizophrenia and unaffected relatives of schizophrenia subjects. Spence et al. [2000], using PET scanning and a letter fluency task, found “qualitatively aberrant patterns of bi-frontal activation” in both schizophrenia patients and obligate genetic carriers of schizophrenia, which differed from the pattern observed in healthy controls. These abnormalities however did not reach statistical significance. The work of Sommer et al. [2001b, 2003] has also revealed decreased lateralization during language production in schizophrenia due to right hemisphere hyperactivation rather than left-lateralized hypoactivation, a finding that has been independently confirmed [Weiss et al., 2006] and which has also been reported in MZ twins discordant for the disorder [Sommer et al., 2004b]. Similarly, during a semantic categorization task, relatives of schizophrenia patients showed significantly greater response in the right inferior frontal gyrus than controls [Whyte et al., 2006]. Increased recruitment of the right homolog of Broca’s area as part of the endophenotype predisposing to schizophrenia is also consistent with the conjecture by Crow that a loss of the normal lateralization for language is a defining feature of this disorder [Mitchell and Crow, 2005], linked not only to functional abnormalities but also to asymmetries in brain structure [Sommer et al., 2001a; Petty, 1999] and neuropsychological profile [Gruzelier, 1999].

We did not find statistically significant differences between bipolar subjects and healthy controls during language production in Broca’s area. Although subjects with bipolar disorder also show reduced performance during

verbal fluency relative to controls, their impairment is significantly less pronounced than that of schizophrenia subjects [Krabbendam et al., 2005]. Because of a relative scarcity of functional neuroimaging studies in bipolar disorder, it is more difficult to place our results in context. However, using a similar overt letter fluency task in a sample of 12 bipolar subjects, Curtis et al. [2007] found increased activation in left frontal areas for bipolar subjects relative to healthy controls. We could not verify a similar effect in our present sample, but we note that the region previously reported was centered in left dorsolateral prefrontal cortex and extended only marginally to the most apical part of Broca’s area. Importantly for the specificity of our findings, neither that report [Curtis et al., 2007] nor an earlier one by our group [Curtis et al., 2001] found significant differences between bipolar subjects and controls in right inferior frontal areas. Current evidence, however, increasingly supports an overlap in genetic risk factors between schizophrenia and bipolar disorder [Cardno et al., 2002; Owen et al., 2007]. In this view, susceptibility genes result in increased risk for both disorders, although with some specificity towards either bipolar or schizophrenia phenotypes [Murray et al., 2004; Owen et al., 2007]. As our results suggest that inferior frontal functional abnormalities during verbal fluency may be part of the schizophrenia, but not bipolar endophenotype, a prediction from the present work would be that inferior frontal abnormalities would be found in carriers of genes predisposing towards the schizophrenia rather than the bipolar phenotype [Harrison and Weinberger, 2005].

A marker of genetic risk for schizophrenia, but not bipolar disorder, may also have clinical utility. Because we found increased recruitment of inferior frontal cortex in the nonpsychotic cotwins of patients with schizophrenia and patients with the disorder, our results are not likely to be a consequence of chronicity or treatment with antipsychotic medication and could potentially be replicated in unmedicated, first episode patients. Confirming our results

in this subpopulation would be important to support the use of inferior frontal abnormalities for the differential early diagnosis of schizophrenia and bipolar disorder. Furthermore, given that according to our results frontal functional abnormalities depend on genetic risk and on diagnosis, they constitute a potential marker for transition to psychosis in high-risk subjects [Yung et al., 1998]. Such diagnostic and prognostic decisions, based on the pattern of activation during verbal fluency, could benefit from recent advances on subject-level classification based on fMRI activation maps [Fu et al., 2008; Marquand et al., 2004].

Several caveats must be taken into consideration when interpreting our findings. The patients included in our study were maintained in their usual medication, resulting in a high proportion of subjects with schizophrenia on antipsychotics. Although, as mentioned earlier, the similar pattern of activation in MZ cotwins of schizophrenia patients suggest that the findings are not due to confounding by medication, the exclusion of such an effect requires replication in an unmedicated sample. Our analysis was also limited to fMRI response in inferior frontal cortex. This region is a key node in language production, and one where previous evidence existed of abnormalities in schizophrenia subjects and unaffected relatives. We employed in our analysis a cytoarchitectonic probabilistic map of the area [Amunts et al., 1999], allowing for accurate and reproducible mapping of the region of interest [Eickhoff et al., 2006]. Other regions involved in normal verbal fluency include anterior cingulate, left parietal and thalamus [based on a meta-analysis of 16 studies, Costafreda et al., in press]. It would be worth exploring whether the present results extend to such areas as well or whether this phenomenon is specific of the inferior frontal cortex.

Additionally, although the different diagnostic groups were similar in key aspects such as IQ and performance, there were differences in age and gender balance, in part reflecting the fact that in the general population, schizophrenia tends to be diagnosed at a younger age than bipolar disorder. There is some evidence that language-related lateralization of fMRI response may be related to age and gender [Shaywitz et al., 1995; Springer et al., 1999], and although such dependency has been disputed [Sommer et al., 2004a], we decided to include these variables as covariates in our analysis. It would be important, however, to reproduce our analysis in a more balanced sample. Finally, the number of MZ twins of schizophrenia and bipolar subjects was modest, resulting in limited power.

A key question is the functional significance of increased recruitment of inferior frontal cortex during language processing in schizophrenia and unaffected identical twins. It is well established that lesions to the left inferior frontal cortex impair language production [Baldo et al., 2006; Damasio, 1992; Stuss et al., 1998, 2003]. The right inferior frontal cortex has often been linked to language comprehension, and in particular to the semantic and emotional decoding of natural language [Buchanan et al.,

2000; Jung-Beeman, 2005]. Right frontal areas may also play a role in normal language production, if increased semantic processing is required [StGeorge et al., 1999; Seger et al., 2000], a phenomenon that may be more pronounced in schizophrenia subjects [Whyte et al., 2006]. Recruitment of right frontal regions may thus reflect a tendency for schizophrenia patients and their nonpsychotic MZ cotwins to make increased use of inefficient semantic strategies for word generation during letter fluency, relative to the other groups. Alternatively, the right inferior frontal gyrus is often also recruited for language production when the left hemisphere language areas are damaged, such as in children with early lesions of the left hemisphere [Liegeois et al., 2004] or adult patients with production aphasia [Price and Crinion, 2005]. Interestingly, higher task difficulty and processing demands in healthy volunteers may also lead to increased Broca's engagement and mobilization of its right homolog [Just et al., 1996], suggesting that bilateral activation in schizophrenia subjects and nonpsychotic cotwins may be linked to increased perceived task difficulty in these subjects relative to healthy participants, or a consequence of impaired or inefficient processing in the normally left lateralized sites of language production.

Our findings cannot be simplified in terms of "hyperfrontality" alone. Because schizophrenia patients typically produce fewer correct words than healthy subjects, greater inferior frontal activation in schizophrenia may be neutralized or even reversed if differences in task performance are not taken into account, through individual-level matching and analytical adjustment. A similar effect, whereby activation in frontal areas is modulated by performance has already been identified when comparing schizophrenia and controls during working memory [Karlsgodt et al., 2007; Thermenos et al., 2005] and semantic fluency [Ragland et al., 2008], and may explain some of the inconsistencies in the previous functional imaging literature on letter fluency in schizophrenia as both increases [Razafiman-dimby et al., 2007; Schaufelberger et al., 2005; Sommer et al., 2001b, 2003; Weiss et al., 2006] and decreases [Boksmann et al., 2005; Curtis et al., 1998; Fitzgerald et al., 2007; Fu et al., 2005; Jones et al., 2004] in activation for patients with schizophrenia relative to controls have been found.

CONCLUSIONS

We observed increased recruitment of the inferior frontal cortex during word production in a large sample of patients with schizophrenia and their unaffected MZ cotwins, which can be interpreted as compensatory recruitment to remediate physiological brain inefficiencies. Increased activation of the right homolog of Broca's area was also present in unaffected twins of schizophrenia subjects, but not in healthy controls, patients with bipolar disorder or their unaffected MZ twins, suggesting that increased recruitment of the inferior frontal gyrus during

verbal fluency may be part of the genetically-mediated endophenotype predisposing to schizophrenia.

REFERENCES

- Altman EG, Hedeker D, Peterson JL, Davis JM (1997): The Altman Self-Rating Mania Scale. *Biol Psychiatry* 42:948–955.
- Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K (1999): Broca's region revisited: Cytoarchitecture and intersubject variability. *J Comp Neurol* 412:319–341.
- Andreasen NC (1983): Scale for the Assessment of Negative Symptoms. Iowa City: University of Iowa.
- Andreasen NC (1984): Scale for the Assessment of Positive Symptoms. Iowa City: University of Iowa.
- Annett M (1970): A classification of hand preference by association analysis. *Br J Psychol* 61:303–321.
- Arts B, Jabben N, Krabbendam L, van Os J (2007): Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med* 38:771–785.
- Baldo JV, Schwartz S, Wilkins D, Dronkers NF (2006): Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *J Int Neuropsychol Soc* 12:896–900.
- Bearden CE, van Erp T GM, Thompson PM, Toga AW, Cannon TD (2007): Cortical mapping of genotype-phenotype relationships in schizophrenia. *Hum Brain Mapp* 28:519–532.
- Beck AT, Steer RA, Garbin MG (1989): Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev* 8:77–100.
- Benton A, Hamsher K, Sivan A (1994): Multilingual Aphasia Examination, 3rd ed. Iowa City, IA: AJA Associates. 30 p.
- Boksman K, Theberge J, Williamson P, Drost DJ, Malla A, Densmore M, Takhar J, Pavlosky W, Menon RS, Neufeld RWJ (2005): A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophr Res* 75:247–263.
- Bora E, Yucel M, Pantelis C: Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord* (in press).
- Bowman F, Caffo B, Bassett SS, Kilts C (2008): A Bayesian hierarchical framework for spatial modeling of fMRI data. *Neuroimage* 39:146–156.
- Buchanan TW, Lutz K, Mirzazade S, Specht K, Shah NJ, Zilles K, Jancke L (2000): Recognition of emotional prosody and verbal components of spoken language: An fMRI study. *Brain Res Cogn Brain Res* 9:227–238.
- Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinski B, Weinberger DR (2003a): Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 160:709–719.
- Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003b): Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. *Am J Psychiatry* 160:2209–2215.
- Cardno AG, Rijdsdijk FV, Sham PC, Murray RM, McGuffin P (2002): A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry* 159:539–545.
- Costafreda SG, Fu CHY, Lee L, Everitt B, Brammer MJ, David AS (2006): A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Hum Brain Mapp* 27:799–810.
- Costafreda SG, David AS, Brammer MJ (2009): A parametric approach to voxel-based meta-analysis. *Neuroimage* 46:115–122.
- Curtis VA, Bullmore ET, Brammer MJ, Wright IC, Williams SC, Morris RG, Sharma TS, Murray RM, McGuire PK (1998): Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. *Am J Psychiatry* 155:1056–1063.
- Curtis VA, Dixon TA, Morris RG, Bullmore ET, Brammer MJ, Williams SC, Sharma T, Murray RM, McGuire PK (2001): Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *J Affect Disord* 66:111–121.
- Curtis VA, Thompson JM, Seal ML, Monks PJ, Lloyd AJ, Harrison L, Brammer MJ, Williams S CR, Murray RM, Young AH, Ferrier IN (2007): The nature of abnormal language processing in euthymic bipolar I disorder: Evidence for a relationship between task demand and prefrontal function. *Bipolar Disord* 9:358–369.
- Damasio AR (1992): Aphasia. *N Engl J Med* 326:531–539.
- Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 25:1325–1335.
- Eickhoff SB, Heim S, Zilles K, Amunts K (2006): Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. *Neuroimage* 32:570–582.
- Fiez JA, Petersen SE (1998): Neuroimaging studies of word reading. *Proc Natl Acad Sci USA* 95:914–921.
- Fitzgerald PB, Sritharan A, Benitez J, Daskalakis ZJ, Jackson G, Kulkarni J, Egan GF (2007): A preliminary fMRI study of the effects on cortical activation of the treatment of refractory auditory hallucinations with rTMS. *Psychiatry Res* 155:83–88.
- Friston KJ, Penny W (2003): Posterior probability maps and SPMs. *Neuroimage* 19:1240–1249.
- Fu CHY, Morgan K, Suckling J, Williams SCR, Andrew C, Vythelingum GN, McGuire PK (2002): A functional magnetic resonance imaging study of overt letter verbal fluency using a clustered acquisition sequence: Greater anterior cingulate activation with increased task demand. *Neuroimage* 17:871–879.
- Fu CHY, Suckling J, Williams S CR, Andrew CM, Vythelingum GN, McGuire PK (2005): Effects of psychotic state and task demand on prefrontal function in schizophrenia: An fMRI study of overt verbal fluency. *Am J Psychiatry* 162:485–494.
- Fu CHY, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SCR, Brammer MJ (2008): Pattern classification of sad facial processing: Toward the development of neurobiological markers in depression. *Biol Psychiatry* 63:656–662.
- Gelman A, Carlin JB, Stern HS, Rubin DB (2004): Bayesian data analysis. Boca Raton, FL: Chapman and Hall/CRC. 668 p.
- Gernsbacher MA, Kaschak MP (2003): Neuroimaging studies of language production and comprehension. *Ann Rev Psychol* 54:91–114.
- Gilks W, Thomas A, Spiegelhalter D (2003): A language and program for complex Bayesian modelling. *Statistician* 43:169–177.
- Glahn DC, Thompson PM, Blangero J (2007): Neuroimaging endophenotypes: Strategies for finding genes influencing brain structure and function. *Hum Brain Mapp* 28:488–501.
- Gottesman II, Gould TD (2003): The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160:636–645.

- Greenland S (2006): Smoothing observational data: A philosophy and implementation for the health sciences. *Int Stat Rev* 74:31–46.
- Gruzelier JH (1999): Functional neuropsychophysiological asymmetry in schizophrenia: A review and reorientation. *Schizophr Bull* 25:91–120.
- Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278–296.
- Harrison PJ, Weinberger DR (2005): Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. *Mol Psychiatry* 10:40–68.
- Heinrichs RW, Zakzanis KK (1998): Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 12:426–445.
- Jones HM, Brammer MJ, O'Toole M, Taylor T, Ohlsen RI, Brown RG, Purvis R, Williams S, Pilowsky LS (2004): Cortical effects of quetiapine in first-episode schizophrenia: A preliminary functional magnetic resonance imaging study. *Biol Psychiatry* 56:938–942.
- Jung-Beeman M (2005): Bilateral brain processes for comprehending natural language. *Trends Cogn Sci* 9:512–518.
- Just MA, Carpenter PA, Keller TA, Eddy WF, Thulborn KR (1996): Brain activation modulated by sentence comprehension. *Science* 274:114–116.
- Karlsgodt KH, Glahn DC, van Erp TGM, Therman S, Huttunen M, Manninen M, Kaprio J, Cohen MS, Linnqvist J, Cannon TD (2007): The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophr Res* 89:191–197.
- Krabbendam L, Arts B, van Os J, Aleman A (2005): Cognitive functioning in patients with schizophrenia and bipolar disorder: A quantitative review. *Schizophr Res* 80:137–149.
- Lezak MD (1995): *Neuropsychological Assessment*, 3rd ed. New York: Oxford University Press. pp. 544–546; 1016 p.
- Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, Baldeweg T (2004): Language reorganization in children with early-onset lesions of the left hemisphere: An fMRI study. *Brain* 127:1229–1236.
- Marquand AF, Mourao-Miranda J, Brammer MJ, Cleare AJ, Fu CHY (2008): Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *Neuroreport* 19:1507–1511.
- McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E, Murray RM (2004): Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry* 61:974–984.
- McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2005): Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. *Br J Psychiatry* 186:378–385.
- Mitchell RLC, Crow TJ (2005): Right hemisphere language functions and schizophrenia: the forgotten hemisphere? *Brain* 128:963–978.
- Mumford JA, Nichols T (2006): Modeling and inference of multi-subject fMRI data. *IEEE Eng Med Biol Mag* 25:42–51.
- Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C (2004): A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res* 71:405–416.
- Nelson HE (1983): *National Adult Reading Test (NART): Test Manual*. Windsor, UK: National Foundation for Educational Research.
- Owen MJ, Craddock N, Jablensky A (2007): The genetic deconstruction of psychosis. *Schizophr Bull* 33:905–911.
- Petty RG (1999): Structural asymmetries of the human brain and their disturbance in schizophrenia. *Schizophr Bull* 25:121–139.
- Pinheiro JC, Bates DM (2000): *Mixed-effects models in S and S-PLUS. Statistics and computing*. New York: Springer. 521 p.
- Plummer M (2003): JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling. In: Hornik K, Leisch D, Zeileis A, editors. *Proceedings of the 3rd International Workshop on Distributed Statistical Computing*. Vienna: Technische Universität Wien. pp 1–10.
- Price CJ, Crinion J (2005): The latest on functional imaging studies of aphasic stroke. *Curr Opin Neurol* 18:429–434.
- Ragland JD, Moelter ST, Bhati MT, Valdez JN, Kohler CG, Siegel SJ, Gur RC, Gur RE (2008): Effect of retrieval effort and switching demand on fMRI activation during semantic word generation in schizophrenia. *Schizophr Res* 99:313–323.
- Razafimandimby A, Maiza O, Herve P-Y, Lecardeur L, Delamillieure P, Brazo P, Mazoyer B, Tzourio-Mazoyer N, Dollfus S (2007): Stability of functional language lateralization over time in schizophrenia patients. *Schizophr Res* 94:197–206.
- Schaufelberger M, Senhorini MCT, Barreiros MA, Amaro EJ, Menezes PR, Sczufca M, Castro CC, Ayres AM, Murray RM, McGuire PK, Busatto GF (2005): Frontal and anterior cingulate activation during overt verbal fluency in patients with first episode psychosis. *Rev Bras Psiquiatr* 27:228–232.
- Seger CA, Desmond JE, Glover GH, Gabrieli JD (2000): Functional magnetic resonance imaging evidence for right-hemisphere involvement in processing unusual semantic relationships. *Neuropsychology* 14:361–369.
- Shaywitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK, Bronen RA, Fletcher JM, Shankweiler DP, Katz L (1995): Sex differences in the functional organization of the brain for language. *Nature* 373:607–609.
- Snitz BE 3rd, Macdonald AW, Carter CS (2006): Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophr Bull* 32:179–194.
- Sommer I, Aleman A, Ramsey N, Bouma A, Kahn R (2001a): Handedness, language lateralisation and anatomical asymmetry in schizophrenia. *Br J Psychiatry* 178:344–351.
- Sommer IE, Ramsey NF, Kahn RS (2001b): Language lateralization in schizophrenia, an fMRI study. *Schizophr Res* 52:57–67.
- Sommer IEC, Ramsey NF, Mandl RCW, Kahn RS (2003): Language lateralization in female patients with schizophrenia: An fMRI study. *Schizophr Res* 60:183–190.
- Sommer I EC, Aleman A, Bouma A, Kahn RS (2004a): Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain* 127:1845–1852.
- Sommer IEC, Ramsey NF, Mandl R CW, van Oel CJ, Kahn RS (2004b): Language activation in monozygotic twins discordant for schizophrenia. *Br J Psychiatry* 184:128–135.
- Spence SA, Liddle PF, Stefan MD, Hellewell JS, Sharma T, Friston KJ, Hirsch SR, Frith CD, Murray RM, Deakin JF, Grasby PM (2000): Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *Br J Psychiatry* 176:52–60.

- Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PS, Brewer CC, Perry HM, Morris GL, Mueller WM (1999): Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. *Brain* 122:2033–2046.
- StGeorge M, Kutas M, Martinez A, Sereno MI (1999): Semantic integration in reading: Engagement of the right hemisphere during discourse processing. *Brain* 122:1317–1325.
- Stuss DT, Alexander MP, Hamer L, Palumbo C, Dempster R, Binns M, Levine B, Izukawa D (1998): The effects of focal anterior and posterior brain lesions on verbal fluency. *J Int Neuropsychol Soc* 4:265–278.
- Stuss DT, Murphy KJ, Binns MA, Alexander MP (2003): Staying on the job: The frontal lobes control individual performance variability. *Brain* 126:2363–2380.
- Szoke A, Schurhoff F, Mathieu F, Meary A, Ionescu S, Leboyer M (2005): Tests of executive functions in first-degree relatives of schizophrenic patients: A meta-analysis. *Psychol Med* 35:771–782.
- Thermenos HM, Goldstein JM, Buka SL, Poldrack RA, Koch JK, Tsuang MT, Seidman LJ (2005): The effect of working memory performance on functional MRI in schizophrenia. *Schizophr Res* 74:179–194.
- Toulopoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, Murray R (2007): Substantial genetic overlap between neurocognition and schizophrenia: Genetic modeling in twin samples. *Arch Gen Psychiatry* 64:1348–1355.
- Wechsler D (1999): Wechsler abbreviated scale of intelligence (WAIS). San Antonio, TX: Harcourt Assessment.
- Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Felber S, Fleischhacker WW (2006): Language lateralization in unmedicated patients during an acute episode of schizophrenia: A functional MRI study. *Psychiatry Res* 146:185–190.
- Whyte M-C, Whalley HC, Simonotto E, Flett S, Shillcock R, Marshall I, Goddard NH, Johnstone EC, Lawrie SM (2006): Event-related fMRI of word classification and successful word recognition in subjects at genetically enhanced risk of schizophrenia. *Psychol Med* 36:1427–1439.
- Young RC, Biggs JT, Ziegler VE, Meyer DA (1978): A rating scale for mania: Reliability, validity and sensitivity. *Br J Psychiatry* 133:429–435.
- Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ (1998): Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl* 172:14–20.

APPENDIX: SPATIAL BAYESIAN HIERARCHICAL MODEL

The reader is referred to Bowman et al. [2008] for the original presentation of the spatial Bayesian hierarchical model for fMRI data. In the following, we will focus on the modifications that we have introduced to their model to reflect the clustered nature of our subject sample.

After first-level analysis using SPM2 and masking using the SPM Anatomy Toolbox [Eickhoff et al., 2005], the input for the multi-subject modeling process is a masked effect size map per subject i ($i = 1, 2, \dots, 132$) for each task difficulty j ($j = 1, 2$; indexing easy and difficult letters), reflecting the voxel-wise estimates of BOLD response changes

during word production relative to the baseline. Each masked effect size map is parcellated in G regions, indexed by $g = 1, \dots, G$ (in our application, $G = 4$ with BA 44 and 45, right and left). The number of voxels for region g is represented by V_g . We will then express the parcellated effect size maps from first-level modeling for subject i performing subtask j as $\beta_{ij,g}$, with distribution:

$$\beta_{ij,g} \sim \text{Normal}(\mu_{ij,g}, \sigma_g^2 \mathbf{I}) \quad (\text{A1})$$

$$\mu_{ij,g} = \mathbf{X}'_{ij} \mathbf{B}_g + a_{\text{twin}(i),g} + a_{\text{ind}(i),g}$$

In other words, the expectation of $\beta_{ij,g}$ is $\mu_{ij,g}$, itself a linear function of the relevant fixed and random effects. $\mathbf{X}_{ij}$ is a column vector containing the quantities associated with the explanatory variables and $\mathbf{B}_g$ contains the unknown maps of fixed effects parameters to be estimated from the data.

Letting $k = 1, \dots, K$ index the fixed effects, then $\mathbf{B}_g = (\mathbf{b}_{1g}, \dots, \mathbf{b}_{Kg})'$, where each $\mathbf{b}_{kg} = (b_{kg}(1), \dots, b_{kg}(V_g))'$. The prior distribution for a given fixed effect k is:

$$\mathbf{b}_{kg} \sim \text{Normal}(\mathbf{1}\gamma_{kg}, \lambda_{kg}^2 \mathbf{I}) \quad (\text{A2})$$

In our application, we included fixed effects terms for sex and age (as a centered continuous variable), diagnostic group, task difficulty, and output (i.e., the number of valid responses), in addition to an intercept effect. The hyperpriors for the fixed effects are given by:

$$\lambda_{kg}^{-2} \sim \text{Gamma}(e_0, f_0) \quad (\text{A3})$$

$$\gamma_{kg} \sim \text{Normal}(n_0, p_0)$$

The terms $a_{\text{twin}(i),g}$ and $a_{\text{ind}(i),g}$ in Eq. (1) represent the twin and individual random effects. In the following explanation, we will focus on the twin effect, but analogous prior distributions were assumed for the individual random effect. The grouping factor $\text{twin}(i)$ allocates subject i to its specific twin set. Defining $\mathbf{a}_{\text{twin}(i)} = (a_{\text{twin}(i)1}, \dots, a_{\text{twin}(i)G})$, the prior and hyperpriors distributions for the twin random effect are given by:

$$\mathbf{a}_{\text{twin}(i)} \sim \text{Normal}(0, \mathbf{\Gamma}_{\text{twin}}) \quad (\text{A4})$$

$$\mathbf{\Gamma}_{\text{twin}}^{-1} \sim \text{Wishart}((h_0 \mathbf{H}_{\text{twin},0})^{-1}, h_0)$$

Finally the error term σ_g^2 in Eq. (1) represents the residual or random variation, after accounting for all the fixed and other random effects in the model, with prior distribution:

$$\sigma_g^{-2} \sim \text{Gamma}(c_0, d_0) \quad (\text{A5})$$

We chose weakly informative (i.e., high variance or equivalently, low precision) priors by setting $c_0 = d_0 = e_0 = f_0 = 0.001$, $n_0 = 0$ and $p_0 = 1000$. We set the degrees of freedom h_0 of the Wishart distribution to $G = 4$ (i.e., the

rank of Γ_{twin}), representing vague prior knowledge. For $\mathbf{H}_{\text{twin},0}$, in an analog approach to Bowman et al. [2008] we used the sample variance–covariance matrix for each random effect computed from the mean effect size estimates for each region.

Bayesian models were coded using the Bayesian Inference Using Gibbs Sampling (BUGS) language [Gilks et al., 2003], and fitted using a C++ MCMC inference engine [Plummer, 2003]. The MCMC chain updated at a

speed of over 5,000 iterations/h on a Linux machine with 2.4 GHz and 8 GB of RAM memory. Samples from the joint posterior distribution were drawn from 100,000 iterations after a burn-in period of 50,000 iterations. Convergence diagnoses were run by inspection of trace plots of all area-level parameters and of randomly chosen voxel-level parameters. The samples were then used to compute summaries of the fixed effect images $\mathbf{b}_{kg}$.