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Functional MR Imaging of Confounded Hypofrontality

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Abstract: Comparatively reduced blood flow to frontal brain regions in patients with schizophrenia (hypofrontality) has been frequently observed in the last 25 years. However, there is an inconstant quality to hypofrontality, suggesting either confounded observation of a static (trait-like) abnormality, or that it is a genuinely dynamic (state-like) phenomenon. Possible confounds in functional magnetic resonance imaging (fMRI) studies of hypofrontality are classified. Methods for assessment and correction of stimulus correlated motion (an extracerebral confound) are reviewed in the context of fMRI data acquired from five schizophrenic patients and five comparison subjects during performance of a verbal fluency task. Factorial analysis of these and other data, acquired from the same subjects during a semantic decision task, is used to exclude a number of possible intracerebral confounds. By analogy to the historical controversy concerning the appearance of the planet Saturn viewed through early telescopes, understanding the inconstancy of hypofrontality in schizophrenia is likely to progress more by theoretically driven experiments that exploit the repeatability of fMRI than by further technological development alone. *Hum. Brain Mapping 8:86–91, 1999.* © 1999 Wiley-Liss, Inc.

Key words: schizophrenia; frontal cortex; factorial design; head movement; permutation test

INTRODUCTION

Hypofrontality is most often used to mean reduced blood flow to frontal brain regions in patients with schizophrenia. This was first demonstrated by Ingvar and Franzen [1974] using clearance of intra-arterial xenon to estimate regional cerebral blood flow (rCBF). Hypofrontality now enjoys almost axiomatic status in psychiatric imaging research: replicated by 60% of subsequent resting rCBF studies and by 90% of positron emission tomography (PET) studies using cognitive activation designs [Weinberger and Berman, 1996].

It is clear that hypofrontality does not carry precisely the same meaning throughout this literature. Sometimes, as originally intended by Ingvar and Franzen [1974], it denotes a reduction in the ratio of frontal to posterior rCBF in patients with schizophrenia. Recently, it has been more widely used to mean simply reduction of task-related frontal rCBF, and, with the advent of functional magnetic resonance imaging (fMRI), it has been generalised to describe reduction in magnitude of task-related frontal signals that are determined more by blood oxygenation than blood flow. It is also now clear that hypofrontality is not pathognomonic of schizophrenia, e.g., we recently demonstrated reduced power of frontal activation using fMRI in groups of patients with autism [Baron-

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Cohen et al., 1999; Ring et al., 1999] and attention deficit-hyperactivity disorder [Rubia et al., 1999].

Besides these questions of terminology and specificity, there is also the issue of phenomenal inconstancy. A number of case-control studies of schizophrenia have *not* demonstrated hypofrontality. More intriguingly, some studies making repeated measurements on the same sample of patients have demonstrated hypofrontality on one occasion but not another [Spence et al., 1998]. In light of these data, the question arises: is hypofrontality genuinely a dynamic or state-like phenomenon, or are we making confounded observations of an essentially static or trait-like abnormality? In favour of a trait model, there are psychological data indicating chronically enduring deficits of executive function in patients with schizophrenia; but a trait model of hypofrontality might imply an anatomical substrate in frontal cortex, and this has so far proved elusive.

CLASSIFICATION OF CONFOUNDS

Functional MR imaging studies of patient groups are potentially confounded by multiple factors, which can be classified according to the scheme shown in Figure 1. Here, the experimental design *D* induces a change in activity of a neuronal population *N* in frontal cortex, which in turn causes a vascular response *V* measured by the imaging system *I*. The preferred or cardinal explanation for hypofrontality is generally that the schizophrenic disease process Sz has directly impaired the capacity of the neuronal population to respond to the experimentally designed task. For example, hypofrontality might be regarded as compatible with histopathological evidence for reduced neuronal number or size, or abnormal cytoarchitectonics, in frontal cortex. However, there are several other mechanisms by which schizophrenia, or its treatment Φ, might reduce task-related variance in imaging data. First, there are *intracerebral* confounds, which may be described as upstream or downstream of the neuronal population of interest. Upstream intracerebral confounds include global cognitive factors such as attention or IQ, as well as disease effects on posterior brain regions and/or their connections with frontal cortex. Possible downstream confounds include modulation of neurovascular coupling by antipsychotic drugs. In this respect, the recent demonstration of dopaminergic nerve terminals in close apposition to intracortical arterioles is highly relevant [Krimer et al., 1998]. Second, there are *extracerebral* confounds that can arise when a systemic effect *S* on variance in imaging data is conditional on the disease or its treatment.

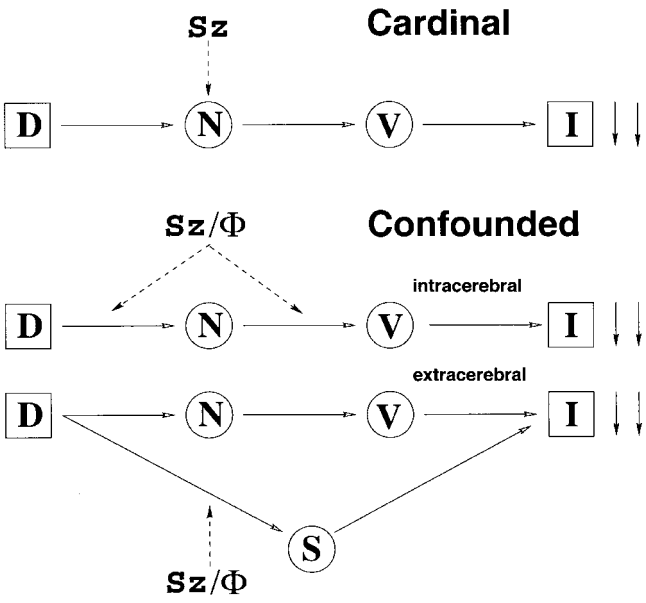

Figure 1.
Schematic classification of cardinal and confounding factors causing hypofrontality in functional imaging studies of schizophrenia.

Here, we review results of some recent studies of schizophrenia that illustrate methods for assessing and correcting the extracerebral confound of stimulus correlated motion [Bullmore et al., 1999b; Curtis et al., 1998] and demonstrate how factorially designed experiments can be used to exclude possible confounds as likely explanations for observed hypofrontality [Curtis et al., 1999].

METHODS AND MATERIALS

Subjects

Five male right-handed patients with schizophrenia diagnosed by standard (DSM-IV) criteria and five male right-handed healthy volunteers were studied. The groups were matched for age and IQ. The patients were high-functioning individuals receiving atypical antipsychotic medication in a specialist treatment unit.

Data acquisition

Gradient echo EPI data depicting T2*-weighted blood-oxygen-level-dependent (BOLD) contrast were acquired at 1.5 Tesla using a GE Signa system: TE = 40

ms, TR = 3 s, in-plane resolution 3 mm, slice thickness 5.5 mm.

Experimental designs

Each subject was scanned twice in the same session under different experimental conditions. Both experiments had a blocked periodic design, in which 30-s epochs of an activation (A) condition were periodically alternated with 30-s epochs of a baseline (B) condition. There were five cycles of BA alternation over the course of each 5-min experiment.

Covert verbal fluency

A: the subject was cued by auditory presentation of a letter, e.g., "F," with interstimulus interval (ISI) = 2.5 s, to generate and subvocally articulate a word beginning with that letter. B: the subject was cued by auditory presentation of the word "rest" with ISI = 2.5 s to subvocally articulate that word.

Covert semantic decision

A: the subject was cued by visual presentation of a word, e.g., "goat," with ISI = 2.5 s, to decide whether the word denoted a living or nonliving object and to subvocally articulate the decision. B: the subject fixated on an isoluminant screen.

Data analysis overview

Movement of the head in three dimensions was estimated and corrected in each individual dataset by a two-stage procedure of realignment [Brammer et al., 1997] followed by regression on the following model [Bullmore et al., 1999b]:

$$\begin{aligned} S_t = {} & \beta_1\delta x_t + \beta_2\delta(x_t)^2 + \beta_3\delta y_t + \beta_4\delta(y_t)^2 + \beta_5\delta z_t \\ & + \beta_6(\delta z_t)^2 + \beta_7\delta x_{t-1} + \beta_8(\delta x_{t-1})^2 + \beta_9\delta y_{t-1} \\ & + \beta_10(\delta y_{t-1})^2 + \beta_{11}\delta z_{t-1} + \beta_{12}(\delta z_{t-1})^2 \\ & + \beta_0 + Y_t \end{aligned} \quad (1)$$

Here, S_t denotes the MR signal at time point t at a given voxel; δ_{x_t}, δ_{y_t}, and δ_{z_t} denote instantaneous positional displacements of that voxel from the image centre of gravity; and $\delta_{x_{t-1}}$, $\delta_{y_{t-1}}$, and $\delta_{z_{t-1}}$ denote positional displacements of the voxel at the time of acquiring the preceding image in the series. The residual series $\{Y_t\}$ is uncorrelated with estimated rigid body motion of the subject's head in 3D.

The power of periodic signal change at the frequency of BA alternation ω was estimated in each motion-corrected fMRI time series $\{Y_t\}$ by sinusoidal regression, using iterated (pseudogeneralised) least-squares to model residual temporal autocorrelation as a first-order autoregressive (AR1) process [Bullmore et al., 1996].

$$\begin{aligned} Y_t = {} & \gamma \sin(\omega t) + \delta \cos(\omega t) + \gamma' \sin(2\omega t) + \delta' \cos(2\omega t) \\ & + \gamma'' \sin(3\omega t) + \delta'' \cos(3\omega t) + \beta_1 t + \beta_0 + \rho_t; \\ \rho_t = {} & \zeta\rho_{t-1} + \epsilon_t \end{aligned} \quad (2)$$

Power at the experimental frequency, i.e., $\gamma^2 + \delta^2$, was divided by its standard error to yield a standardised test statistic P at each voxel, and the resulting P maps were registered in standard space [Brammer et al., 1997]. The main effects of diagnostic group and experimental task and the interactive effect of group × task, on standardised power at each voxel were estimated by fitting analysis of (co)variance (AN[C]OVA) models, described below, and the appropriate null hypotheses were tested by permutation. The permutation procedure is described in detail elsewhere [Bullmore et al., 1999a], but essentially involved estimating the model parameter of interest after repeated random permutation of the appropriate column of the design matrix, and pooling these parameter estimates over voxels to sample the parameter permutation distribution. The critical values for a two-tailed test of size α are then, simply, the $100 \times \alpha/2$ and $100 \times 1 - \alpha/2$ percentiles of the permutation distribution.

RESULTS

Extracerebral confound

The time series of movement parameters, i.e., rotations and translations in {x, y, z}, estimated for each image acquired during the verbal fluency experiment were fitted to the same sinusoidal regression model used to estimate power of functional response, Eq 2. In this case, model parameters were used to derive an estimate of the power of *stimulus correlated motion,* or movement at the experimentally designed frequency. It was clear from these data that the schizophrenic patients were more inclined to move their heads "in time" with the experimental input function. This is illustrated by a plot of the median time series of rotations in {x, y, z} for both groups (see Fig. 2).

The main significance of this between-group difference in stimulus correlated motion is that it will bias

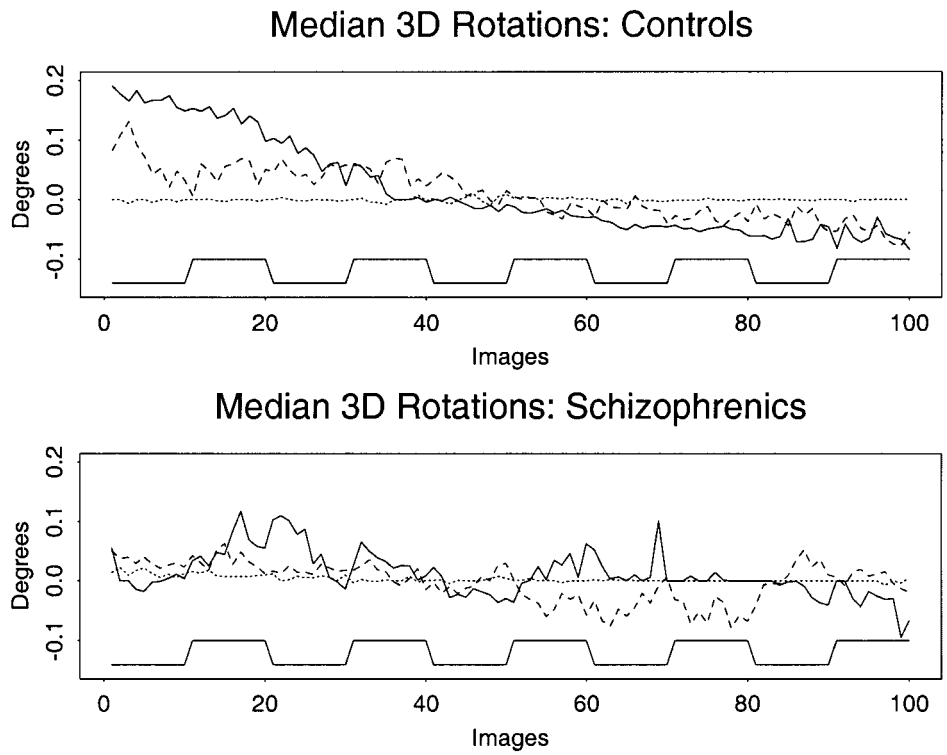

Figure 2.
Time series of 3D rotational displacements (degrees) in control and schizophrenic groups: solid line, x rotation; dashed line, y rotation; dotted line, z rotation. Square wave indicates the experimental design. Periodic x and y rotation at the frequency of the input function is more marked in the schizophrenic data than in the control data.

estimation of any between-group difference in power of functional response. To see this, recall that the image is modelled as a linear function of the design plus error, III = $\beta D + \epsilon$, and our test statistic $P \approx \hat{\beta}/\mathrm{Var}(\epsilon)$. If there is zero stimulus correlated motion, but the subject does move his head in some other way, the effect of fitting Eq 1 to the image will be simply to reduce Var(ϵ), thus increasing the size of the test statistic. However, if there is stimulus correlated motion then the effect of fitting Eq 1 will be to reduce both Var(ϵ) and $\hat{\beta}$, thus potentially decreasing the size of the test statistic. Thus whatever the true difference in power of frontal response between the control and schizophrenic groups, the relative preponderance of stimulus correlated motion in the schizophrenic group can be expected to bias estimation of the difference in the direction of hypofrontality.

To demonstrate this, we first estimated the difference in power of functional response between groups by fitting the following ANOVA model at each voxel:

$$P^a = \beta_0 + \beta_1 G + \epsilon \qquad (3)$$

Here, P^a denotes the standardised power of response at a given voxel *after* motion correction by regression on Eq 1; β_0 is the overall mean power at that voxel; ϵ is a residual term. A total of 735 voxels, mostly located in frontal and parietal cortex, demonstrated significantly reduced power of functional response in the schizophrenic group (permutation test; two-tailed $\alpha = 0.01$).

We also estimated the group difference in functional response by an analysis of covariance (ANCOVA) model, which included a covariate ΔP intended to correct the comparison for variability in stimulus correlation:

$$P^a = \beta_0 + \beta_1 G + \beta_2 \Delta P + \epsilon$$
$$\Delta P = P^b - P^a \qquad (4)$$

Here, P^b denotes the standardised power of response estimated at a given voxel *before* motion correction by regression. The difference between power estimates before and after motion correction ΔP was generally positive in the schizophrenic group due to stimulus

correlated motion and generally negative in the control group. A total of 328 voxels, mostly located in frontal cortex, demonstrated a significant reduction of functional response in the schizophrenic group (permutation test; two-tailed $\alpha = 0.01$).

In short, an analysis of these data that neglected the extracerebral confound of stimulus correlated motion would have substantially exaggerated the evidence for hypofrontality in the schizophrenic group. However, it was possible to estimate and correct the effect of this confound.

Some intracerebral confounds

Studying patients repeatedly under a variety of experimental conditions in the same scanning session, or longitudinally, is ethically acceptable using fMRI and provides a valuable opportunity to narrow the range of possible explanations for hypofrontality. For example, we acquired data from all subjects performing both a covert verbal fluency task and a covert semantic decision task. The results of fitting Eq 4 to the verbal fluency data indicated hypofrontality in the schizophrenic group [Curtis et al., 1998]; the results of fitting the same model to the semantic decision data did not [Curtis et al., 1999]. The null hypothesis that the group (G) by task (T) interaction is zero was more formally assessed by fitting the following ANCOVA model

$$P = \beta_0 + \beta_1 G + \beta_2 T + \beta_3 G \times T + \beta_4 \Delta P + \epsilon \quad (5)$$

and testing the coefficient β_3 by permutation. A total of 471 voxels, mostly located in frontal cortex, demonstrated a significant interactive effect (permutation test; two-tailed $\alpha = 0.05$) (see Fig. 3).

Taken together, these experiments therefore demonstrate an inconstantly hypofrontal pattern of functional response by the schizophrenic group. However, the basic design principle of making repeated measurements on the same sample allows us to exclude several possible explanations that have been advanced to account for the inconstancy of hypofrontality over all studies in the literature. For example, our result obviously cannot be attributed to sampling variation, heterogeneity of the disorder, or variability in scanning or analysis procedures. It is also most unlikely to be due to intracerebral confounds such as antipsychotic drug treatment, symptom state, or global cognitive factors, since these can all be assumed to remain constant over the scanning session. The most plausible remaining explanations are that hypofrontality is accentuated when patients are asked to perform a difficult task, and the semantic decision experiment was too easy to cause decompensation of frontal function, and/or that there is pathological damage to task-specific processing hierarchies culminating in frontal cortex rather than a circumscribed lesion to frontal cortex alone.

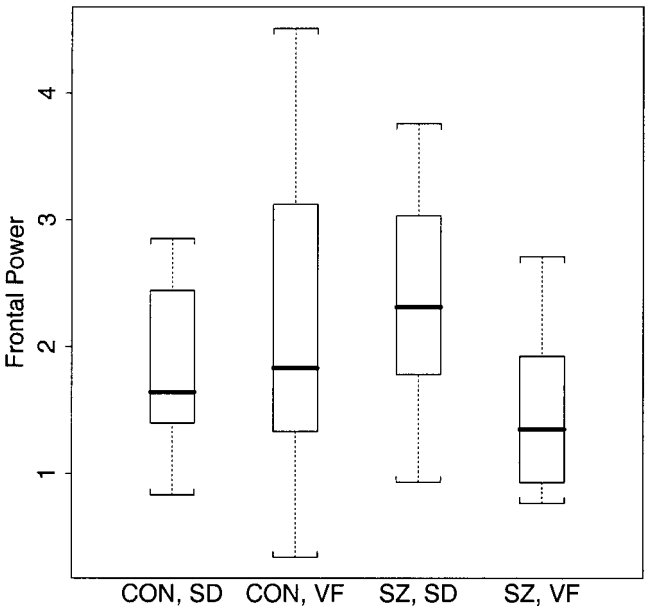

Figure 3.
Inconstancy of hypofrontality. Box-and whisker plots showing regional mean power of frontal response, estimated for each subject by averaging *P* over all frontal lobe voxels demonstrating a significant interactive effect of group by task by Eq.5. Mean power of response by the control group (CON) is similar for both verbal fluency (VF) and semantic decision (SD) tasks. The schizophrenic group (SZ) demonstrates relatively reduced power of frontal response to the verbal fluency task and relatively increased power in response to the semantic decision task.

DISCUSSION

Hypofrontality in schizophrenia is not an observation that was strongly predicted before it was made. It is arguably still a theoretically unconstrained product of technological development in brain imaging. It might be natural to wonder whether further technological development alone will be sufficient to resolve its unfortunately evanescent quality, e.g., might we be able unfailingly to demonstrate hypofrontality by scanning at 3 or 4 Tesla rather than the lower field strengths more widely used at present?

There is an analogous episode in the history of astronomy that may shed some light on this question. In the late sixteenth century, a new-fangled imaging

device became available for the first time, thanks to technological development in optics. Astronomers were able to look at the planets through a telescope, but what they saw when they looked at the planet Saturn was both unpredicted and the subject of disagreement between them. The planet was obviously not always a perfect disc, as had been expected, but it was not obvious how it should be regarded instead. Different astronomers mapped it as a circle flanked by two smaller circles, or two triangles, or one or two crescents [see Tufte, 1997 for illustration]. Strangely, its appearance was also noted to change between observations by the same astronomers. This phenomenal inconstancy was ultimately resolved not by the development of much better telescopes, but by the development of a much better theoretical model for the observations. Christian Huygens understood that Saturn was constantly surrounded by rings and that its inconstant appearance viewed through a telescope was the result of a confounding interaction between the different orbits of Saturn and Earth around the Sun.

The point of this story is consistent with the data reviewed here. Functional MRI represents a major technological development, but it does not automatically clarify phenomena. It may even introduce new sources of bias in their estimation, such as stimulus correlated motion. However, the repeatability of fMRI does provide a potentially powerful weapon against confounded observation that, combined with theory, may move psychiatric imaging research closer to a Huygensesque resolution of the inconstancies of hypofrontality.

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