BRIEF REPORT

# Frontal and anterior cingulate activation during overt verbal fluency in patients with first episode psychosis

# Ativação frontal e do cíngulo anterior durante tarefa de fluência verbal em pacientes em primeiro episódio psicótico

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*Abstract*

***Objective:*** *Functional neuroimaging studies using phonological verbal fluency tasks allow the assessment of neural circuits relevant to the neuropsychology of psychosis. There is evidence that the prefrontal cortex and anterior cingulate gyrus present different activation patterns in subjects with chronic schizophrenia relative to healthy controls. We assessed the functioning in these brain regions during phonological verbal fluency in subjects with recent-onset functional psychoses, using functional magnetic resonance imaging (FMRI).* ***Methods****: Seven patients with functional psychoses (3 schizophreniform, 4 affective) and 9 healthy controls were studied. We compared functional magnetic resonance images acquired during articulation of words beginning with letters classified as easy for word production in Portuguese. Statistical comparisons were performed using non-parametric tests.* ***Results****: There were no differences between patients and controls in task performance. Controls showed greater activation than patients in the left rostral anterior cingulate gyrus and right inferior prefrontal cortex, whereas patients showed stronger activation than controls in a more dorsal part of the anterior cingulate gyrus bilaterally and in a more superior portion of the right prefrontal cortex.* ***Conclusion****: Our preliminary findings of attenuated engagement of inferior prefrontal cortex and anterior cingulate gyrus in patients with recent onset psychosis during phonological verbal fluency are consistent with those of previous studies. The greater activation found in other parts of the anterior cingulate gyrus and prefrontal cortex in patients may be related to a compensatory response that is required to maintain normal task performance, and suggests a pattern of disorganized activity of different functional anterior cingulate gyrus units in association with psychotic conditions.*

***Keywords****: Magnetic resonance imaging; Frontal lobe; Schizophrenia/diagnosis; Speech production measurement; Language tests*

*Resumo*

***Objetivo****: Estudos de neuroimagem funcional empregando tarefa de fluência verbal fonológica têm permitido a avaliação dos circuitos neurais relevantes à neuropsicologia das psicoses. Pacientes com esquizofrenia crônica apresentam diferença nos padrões de ativação em córtex pré-frontal e giro do cíngulo anterior em relação a controles normais. Essas regiões cerebrais foram avaliadas por ressonância magnética funcional, durante tarefa de fluência verbal fonológica, em pacientes com psicose funcional de início recente.* ***Métodos:*** *Sete pacientes com psicose funcional (3 esquizofreniformes, 4 afetivos) e nove controles saudáveis foram estudados. Foram comparadas as imagens de ressonância magnética funcional adquiridas durante a articulação de palavras que começassem com letras classificadas como "fáceis" para a produção de palavras em Português. Comparações estatísticas foram obtidas com métodos não-paramétricos.* ***Resultados****: Os grupos não diferiram em relação ao desempenho da tarefa. Os controles apresentaram maior ativação em cíngulo anterior rostral esquerdo e em córtex pré-frontal inferior direito, enquanto os pacientes mostraram maior ativação em uma região mais dorsal do cíngulo anterior bilateralmente e em uma porção mais superior do córtex pré-frontal direito.* ***Conclusão****: Nossos resultados preliminares são consistentes com estudos prévios e demonstram menor ativação em córtex pré-frontal e cíngulo anterior em pacientes com psicose de início recente durante tarefa de fluência verbal fonológica. A maior ativação em outras partes do cíngulo anterior e do córtex pré-frontal em pacientes pode estar relacionada a uma resposta compensatória necessária para a manutenção do desempenho normal da tarefa e sugere que uma alteração do padrão de atividade das diversas unidades funcionais do cíngulo anterior está associada aos transtornos psicóticos.*

***Descritores****: Imagem por ressonância magnética; Lobo frontal; Esquizofrenia/diagnostico; Medida da produção da fala; Testes de linguagem*

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## Introduction

Subjects with psychosis frequently show impairments in several cognitive domains, including memory, attention and executive functioning.[1] Phonological verbal fluency (PVF) deficits have been particularly well documented in psychosis, and the neural correlates of such impairments have been frequently studied in functional imaging studies.[2-3]

PVF tasks engage brain regions relevant to language production and executive processing, including the prefrontal cortex (PFC) and anterior cingulate gyrus (ACG), and involve operations such as selection of appropriate responses and action monitoring.[4] Prevailing neuropsychological models propose that individuals with psychosis have impairments in these processes and malfunctioning of circuits connecting prefrontal regions, via the anterior cingulate cortex, to the temporal cortex and basal ganglia.[5] Functional imaging studies in healthy subjects have consistently detected activation of the PFC during PVF tasks,[4,6-8] and this has led to the use of such paradigms to investigate "hypofrontality" in patients with psychotic disorders. Some studies have shown reduced activity in the inferior PFC and ACG in subjects with schizophrenia, when compared to healthy controls.[3,9-10] However others have reported normal PFC function, but found a failure to suppress the activity of the superior temporal gyrus[11] or lateralization differences in schizophrenic subjects as compared to controls.[12] Imaging studies of bipolar subjects during PVF tasks have been more scarce, and do not report "hypofrontality" when compared to healthy controls.[13]

Although deficits in executive functioning in psychotic disorders are present since the onset of the illness,[14] to date, the majority of functional imaging studies have investigated subjects with a chronic illness, implying the potential confounding influence of prolonged exposure to neuroleptic medication, multiple psychotic episodes, long hospital stays and severe negative symptoms.

In the present study, we assessed the patterns of cortical activation during an overt PVF task using functional magnetic resonance imaging (fMRI) in subjects with recent-onset functional psychotic disorders, compared to a group of healthy volunteers. Our paradigm involved the presentation of letters with a low degree of difficulty to produce words, in order to allow comparable PVF performance between patients with psychosis and healthy controls. We tested the hypothesis that patients with first-episode psychosis would show reduced activation in the ACG and PFC in relation to controls, independently of differences in task performance.

## Methods

We recruited seven first-episode patients with functional psychosis (3 male; mean age = 30 ± 9.5 years; mean years of education = 10.5 ± 3.0, mean duration of illness = 20 ± 10.4 weeks), who met DSM-IV criteria for schizophreniform disorder (n = 3), psychotic depression (n = 1) or psychotic mania (n = 3). Current symptom severity was assessed by the Positive and Negative Syndrome Scale (PANSS)[15] (mean score in subscales: positive = 8 ± 1.5 and negative = 11 ± 6.6). Three patients had been on antipsychotic drugs for a mean of 63 ± 49 days, one was drug-naïve, and the other three had been drug-free for at least 9 weeks at the time of the scanning (before this, the latter had received 68 ± 38 days of antipsychotic treatment). Nine healthy volunteers, with no personal or first-degree family history of psychiatric disorders, were recruited from the same community as were the patients (3 male, mean age 31 ± 9.3 years, mean years of education = 11.8 ± 3.3). All subjects were right-handed, as assessed by the Annett questionnaire[16] and were Portuguese native speakers. Mean estimated IQ, obtained using the Wechsler Abbreviated Scale of Intelligence,[17] was 95.3 ± 15.2 in controls and 86.8 ± 12.3 in subjects with psychosis (p = 0.24). The research protocol was approved by local ethics committees, and all subjects gave their written informed consent.

Subjects were studied when performing a PVF task involving the overt articulation of words beginning with visually presented cue letters (1250 ms) classified as "easy" in Portuguese,[18] meaning that controls could normally generate a relatively large number of words from these letters (e.g. P, F, M, C, L, B, T). Subjects' overt responses were acquired during the silent period of acquisition (2750 ms) and were recorded on Cool Edit 2000 (Syntrillium Software Corp.), in order to provide information on the subject's task performance. Blocks of letters were contrasted with a control condition consisting of reading aloud the word "nothing" in Portuguese ("*nada*"). Each condition was repeated 5 times, with 7 presentations of a given letter.

A sequence of 105 gradient-echo T2*echo planar images was obtained using a Signa 1.5T scanner (General Electric, Milwaukee WI, USA), as 15 non-contiguous 7mm-thick axial slices, parallel to the intercommisural line (AC-PC) line, with the following parameters: TE 40 msec, TR 2 sec, 64 x 64 pixels, interslice gap 0.7 mm, FOV 20 x 20 mm, flip angle = 90. Stimulus presentation was synchronized with image acquisition via an optical relay, triggered by the radiofrequency pulse.

Image analysis involved, firstly, data realignment[19] to minimize motion related artifacts, and smoothing using a Gaussian filter (FWHM 7.2 mm). Individual activation patterns in response to the tasks were then detected by time-series analysis using Gamma variate functions, convolved separately with 4 and 8 seconds to model the BOLD response. The weighted sum of these two convolutions that gave the best fit to the time series at each voxel was subsequently calculated, and a goodness of fit statistics was computed at each voxel. The ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) was divided by the sum of squares due to the residuals (original time series minus model time series) (SSQratio). In order to sample the SSQratio distribution under the null hypothesis that observed values of SSQratio were not determined by experimental design (with minimal assumptions), the time series at each voxel was permuted using wavelet-based re-sampling.[20-21] This process was repeated 10 times at each voxel and the data combined over all voxels, resulting in 10 permuted parametric maps of SSQratio at each plane for each subject. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data during randomization. The combination of randomized data over all voxels yields the distribution of SSQratio under the null hypothesis. A test that any given voxel is activated at any required type I error can then be performed by obtaining the appropriate critical value of SSqratio from the null distribution. For example, SSQratio values in the observed data lying above the 99$^{th}$ percentile of the null distribution have a probability under the null hypothesis of $< = 0.01$. We have shown that this permutation method gives very good type I error control with minimal assumptions of ditribution.[20-21]

In order to extend statistical inferences to the group level, the observed and randomised SSQratio maps were transformed

into standard space[22] by an affine transformation onto a Talairach template from 30 Subjects.[23] The median SSQratio observed over all subjects in each group were then tested at each intracerebral voxel in standard space[22] against a critical value of the permutation distribution for the median SSQratio, ascertained from the spatially transformed wavelet-permuted data.[23] Finally, for the comparisons of activation patterns between psychotic patients and healthy controls, analysis of variance was accomplished on the SSQratio maps in standard space by first computing the difference in median SSQratio between groups at each voxel. Subsequent inference of the probability of this difference under the null hypothesis was made by reference to the null distribution obtained by repeated random permutation of group membership and recomputation of the difference in median SSQratios between the two groups obtained from the resampling process. Cluster-level maps were then obtained as described above, displayed at $p < 0.05$ (minimum cluster size = 5 voxels).[21]

## Results

There were no differences in the number of errors (absent responses; repetitions of previous responses; words beginning with other letters; proper nouns) between patients with psychoses and controls (mean = 12.4 ± 7.3 versus 10± 9.4, in 35 trials, unpaired t-test = 0.56, p = 0.57).

There was greater activation in controls than patients in 2 clusters in the rostral portion of the left ACG (Brodmann area – BA24/32) and the adjacent part of the left medial frontal gyrus (BA9/8), and in another cluster in the right inferior frontal gyrus (BA47) (Table 1; Figure 1A). Conversely, patients with psychosis showed more activation relative to controls in a cluster spanning the dorsal ACG (BA24/32) bilaterally and the left medial frontal gyrus (BA6), and in a cluster in the right dorsolateral PFC (BA10/46) (Table 1; Figure 1B).

There was also differential activation in areas where we did not predict between-group differences. Psychosis patients showed greater activation in the: left lingual (BA19, 53 voxels), fusiform (BA18, 99 voxels) and middle occipital (BA18/19, 28 voxels) gyri; right (18 voxels) and left (280 voxels) postero-inferior cerebella; and left superior temporal gyrus (BA22/42, 52 voxels) (all $p < 0.05$, corrected at cluster level). Finally, controls showed greater activation relative to psychosis patients in the following additional non-frontal regions: right middle temporal gyrus (BA21/37, 11 voxels); right anterior and postero-superior cerebellum (31 voxels) ($p < 0.05$, corrected at cluster level).

## Discussion

In this preliminary fMRI study, we assessed subjects with recent-onset psychosis compared to healthy controls during PVF testing, with emphasis on the investigation of brain activation patterns in the PFC and ACG.

Our between-group differences indicated a dissociation of the activity of the rostral and dorsal portions of the ACG during PVF performance. The ACG is thought to be critical for initiation of action, selective attention, selection and monitoring of conflicting responses and error detection.[24] ACG abnormalities have been documented in previous neuropathological and functional imaging studies of chronic schizophrenia,[25-28] and ACG dysfunction is compatible with hypotheses of a core deficit in schizophrenia involving a failure to monitor actions generated internally. The rostral ACG, which showed greater VF-related activity in controls relative to patients with psychosis in the present study, coincides with foci of activation identified in previous functional imaging studies in healthy volunteers using VF tasks.[6-7,29] Conversely, our finding of greater activity in a more dorsal ACG portion in subjects with psychosis has not been reported previously. The only previous study of fMRI with first-episode psychosis showed greater activation in this region during performance of the same VF paradigm in English, but using 'hard' than 'easy' letters.[30] Other authors performed a verbal fluency study with first-onset psychosis with SPECT and described a trend to hypofrontality (when the data were analyzed with regions of interest)[31] and a decrease in perfusion in the anterior cingulate (with Statistical parametric Mapping) in the patient group.[32] In healthy subjects, there has been evidence that distinct ACG portions display reciprocal patterns of activation/inhibition during tasks with variable degrees of cognitive/emotional demands.[33] If replicated in further studies, our preliminary finding may suggest a pattern of disorganized activity of different functional ACG units in association with psychotic conditions. In a recent fMRI study, heterogeneous patterns of ACG activation were detected during the Stroop task, which involves selective attention and also response

**Table 1 – Brain regions showing significantly different patterns of activation in prefrontal and anterior cingulate regions in response to a verbal fluency task between 7 first-episode subjects with psychosis and 9 healthy comparison subjects during functional MRI scanning**

| | Cluster size[a] | Cerebral region (Brodmann area - BA) | Coordinate[b] | | | p value[c] |
|---|---|---|---|---|---|---|
| | | | x | y | z | |
| Controls > patients with psychosis | 27 voxels | (L) Rostral anterior cingulate cortex (BA 24/32) | -4 | 33 | 18 | 0.009 |
| | | (L) Medial prefrontal cortex (BA 9) | -4 | 37 | 27 | 0.019 |
| | 14 voxels | (L) Rostral anterior cingulate cortex (BA 32) | -4 | 26 | 36 | 0.008 |
| | | (L) Medial prefrontal cortex (BA 8/9) | -7 | 30 | 39 | 0.006 |
| | 12 voxels | (R) Inferior frontal gyrus (BA45/47) | 43 | 22 | -3 | 0.001 |
| Patients with psychosis > controls | 38 voxels | Medial frontal cortex (BA 6) | 0 | 0 | 48 | 0.0008 |
| | | (L) Dorsal anterior cingulate cortex (BA 24/32) | -4 | 4 | 42 | 0.013 |
| | | (R) Dorsal anterior cingulate cortex (BA 24) | 4 | 4 | 42 | 0.020 |
| | 11 voxels | (R) Middle frontal gyrus (BA10/46) | 32 | 33 | 12 | 0.008 |

*(L) = left hemisphere; (R) = right hemisphere*
*[a] Total number of contiguous voxels in each region which surpassed a statistical threshold of p < 0.05 (corrected).*
*[b] Coordinates of the voxel of maximal statistical significance within each region, according to the atlas of Talairach & Tornoux[22]*
*[c] Level of statistical significance at cluster level (p < 0.05)*

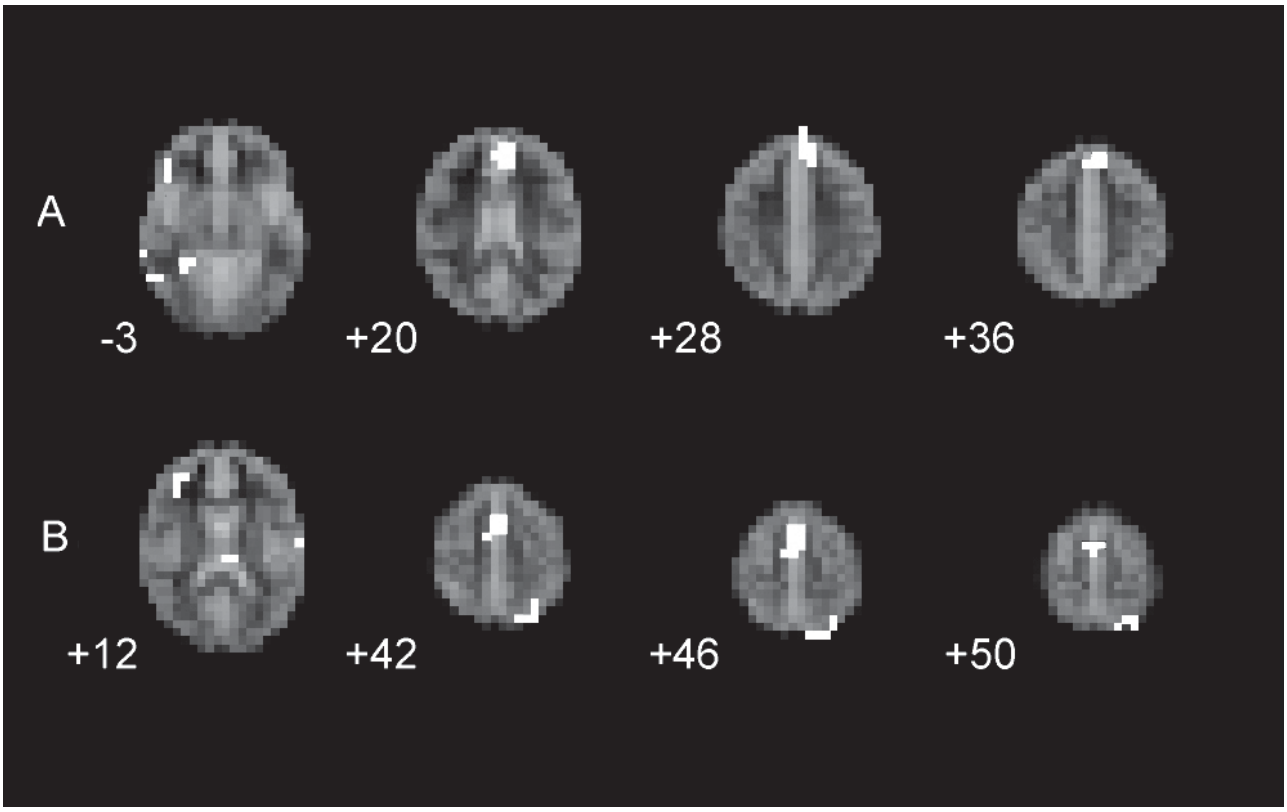


**Figure 1** – Two dimensional representative axial slices are presented with activations displayed on a high-resolution template image. A) areas showing increased activation in healthy subjects compared to psychotic patients during a verbal fluency task with FMRI (right inferior frontal gyrus, left medial frontal gyrus and left rostral anterior cingulate) and B) areas with increased activation in subjects with psychosis when compared to healthy controls (right middle frontal gyrus, a more superior bilateral medial frontal gyrus and bilateral dorsal anterior cingulate) – Anova cluster $p < 0.05$. Numbers in each frame indicate the z coordinate in the standard Talairach coordinates.[22] The clusters are detailed in Table 1. The right side of the images corresponds to the left side of the brain (radiological convention).

selection: the authors reported extensive ACG activation in healthy controls, while patients with chronic schizophrenia showed activation restricted to a dorsal ACG portion similar to the area engaged in the psychosis group in our study.[34]

We found no between-group differences in the left inferior frontal gyrus (IFG), the region most classically involved in PVF tasks (Broca's area). However recent studies of VF in chronic psychosis have indicated that attenuated activation in the IFG is bilateral,[9,35] while others showed no differences between psychosis patients and healthy controls.[11-12] Other previous studies have involved chronic patients samples of modest size, and this may partially explain the heterogeneous findings reported so far. Moreover, in our study, there were both patients with schizophreniform and affective psychoses, and this may have also influenced on the activation patterns detected. On the other hand, we did find other areas of between-group differences in the PFC, including greater activation in the psychosis group in a more superior portion of the right PFC. This may indicate that, in order to maintain adequate VF performance, subjects with psychosis demanded the engagement of different PFC areas compared to healthy controls. This possibility would be consistent with findings of abnormal lateralization in the PFC activation documented in patients with psychosis in previous imaging studies.[12,36] In addition to the above-mentioned limitations, it should also be highlighted that the variable degree of exposure to antipsychotic medication in the psychosis group may have influenced on our between-group differences, considering that there is evidence that the use of typical antipsychotics could reduce metabolism in the brain areas targeted in the present study.[37] On the other hand, one strength of our study was the use of a clustered acquisition imaging protocol, benefiting from the silent periods of acquisition to record verbal responses during the task. The between-group differences in PFC activation and the distinct engagement of different ACG portions in psychosis subjects warrant further investigation in future fMRI studies with larger samples, preferably dichotomizing patients in subgroups with affective and schizophreniform psychoses.

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