MORPHOLOGY OF FRONTO-TEMPORAL REGIONS AND WORD GENERATION IN FIRST-EPISODE SCHIZOPHRENIA

Tomas Kasperek,^{1,*} Hana Kucerova,¹ Radovan Prikryl,¹ Eva Ceskova,¹ Michal Mikl,²
Petr Krupa,³

¹ - Department of Psychiatry, Masaryk University, Faculty of Medicine and Faculty Hospital Brno-Bohunice, Brno, Czech Republic

² - Department of Neurology, Masaryk University, Faculty of Medicine and Faculty hospital St. Anna, Brno, Czech Republic

³ - Department of Imaging Methods, Masaryk University, Faculty of Medicine and Faculty hospital St. Anna, Brno, Czech Republic

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Abstract

Fronto-temporal (FT) dysfunction is a characteristic feature of schizophrenia. We tried to find features of brain morphology that are connected with the solving of Verbal Fluency Task (VFT). We hypothesized that verbal fluency results correlate positively with gray and white matter volume in fronto-temporal areas. 25 first-episode schizophrenia men were tested using VFT. Brain morphology - regional gray and white matter volume was analyzed using optimized voxel-based morphometry. Correlations between VFT score and brain morphology were performed using General linear mode - regression analysis. There was a significant positive correlation of regional gray matter and VFT score in the posterior part of superior temporal gyrus, on the borders with middle temporal gyrus and inferior parietal lobule. As for the regional white matter volume there was one significant cluster in the depth of the inferior frontal gyrus, pars triangularis. The ability to generate context appropriate words is not only the result of abnormal FT co-operation or ability to "hire" prefrontal activity when necessary, but also stems from the condition of relevant neuronal networks.

Key words: voxel-based morphometry, schizophrenia, FT-dysfunction, verbal fluency task

INTRODUCTION

Fronto-temporal (FT) dysfunction is a characteristic feature of schizophrenia. One of the testing paradigms of FT systems co-operation is Verbal fluency task (VFT). Imaging studies of schizophrenia patients show abnormal activation pattern during generation of cued words described as "fronto-temporal disconnection" (Frith et al., 1995). These results are explained in the context of altered prefrontal function, its inability to suppress irrelevant activity of superior temporal gyrus and to support processing of cued words. Not only the function of FT systems seems to be aberrant in schizophrenia - changes of morphology in these areas were replicated several times (Honea et al., 2005). Correlation studies of functional

and morphological features in schizophrenia may shed light on the functional consequences of brain morphology changes in schizophrenia. This approach was already adopted by several groups investigating correlations between brain morphology and executive functions (Bonilha et al., 2008), memory (Antonova et al., 2005), or attention (Salgado-Pineda et al., 2003).

This study was designed to find features of brain morphology that are connected with the solving of VFT. We hypothesized that verbal fluency results correlate positively with gray and white matter volume in fronto-temporal areas.

*Tomas Kasperek, Department of Psychiatry, Masaryk University, Faculty of Medicine and Faculty Hospital Brno-Bohunice, Jihlavska 20, 625 00, Brno, Czech Republic, phone.: +420 53223 2560, fax: +420 53223 3706, e-mail: tomas.kasperek@centrum.cz

METHODS

25 schizophrenia men without the history of neurological or somatic condition with known connection with brain abnormalities underwent Verbal Fluency Task and whole-head MRI examination at the end of the acute phase of the treatment of the first episode. All of them were on the antipsychotic medication according to the clinical needs, with risperidon as the treatment of the first choice. The study was approved by a local ethical board and all subject signed informed consent. Clinical characteristics of the study sample were described by the PANSS scores at the time of MRI assessment, schizophrenia subtype according to the research criteria of ICD 10 classification, duration of the untreated illness, treatment regimens and the duration of the acute phase treatment.

During Verbal fluency task patients were asked to verbalize as much as possible words starting with a given letter during 60 seconds. The task consisted of three blocks with different cues. The total number of words generated during the whole task constituted the score which compared with the standard values gave the level of functioning.

T1 weighted MRI scans from 1,5 T Siemens scanner, with voxel size 1.2x0.47x0.47 mm, were processed according to the optimized protocol of voxel-based morphometry (Good et al., 2001). It includes improved nonlinear spatial normalization using MNI template and extracted brain to avoid the influence of non-brain tissue with similar signal intensity, segmentation of brain tissue into separate gray, white matter and CSF images, modulation step that removes the influence of nonlinear transformation on regional values thus giving the information about particular tissue volume in every voxel and finally smoothing step (with 12 mm FWHM Gaussian kernel) to allow for between subject comparison and to get the data more normally distributed for consequent parametric statistical analysis.

Voxel-wise statistical comparison based on General linear model ("Simple regression") was used to identify positive correlation of regional gray and white matter volume in every voxel and the number of words generated during the VFT. We used total gray and white matter volume and age as nuisance variables to exclude their influence on the relationship of regional volumes with the number of words. The results were considered significant at $p < 0,001$ uncorrected for multiple comparisons. Only clusters larger then 100 consecutive significant voxels were considered.

RESULTS

The mean age of the patients was 23.3 (SD 4.7) years. 20 patients (80%) were hospitalized for Paranoid

schizophrenia and 5 (20%) for Undifferentiated schizophrenia. The mean duration of illness till the onset of treatment was 9.0 months (SD 14.5). 22 patients were right- and 3 left-handers. All patients were treated with 2nd generation antipsychotics. 3 patients were treated with electroconvulsive therapy prior to MRI. 6 patients responded to the second treatment course and 1 patient to the third one. The duration of treatment of the first episode was 51.2 days on average (SD 16.0). The mean scores on the PANSS scale at the end of the first episode treatment, when the MRI examination was done were 9.1 (SD 2.0) for the positive subscale; 16.1 (SD 5.6) for the negative one; 27.4 (SD 6.5) for the general one; while the total score was 52.7 (SD 12.8). The mean change of total PANSS score from the beginning of hospitalization till the end of treatment of the acute phase was -41.8% (SD 20.0).

The mean VFT score was 39.7 (SD 13.9) words, corresponding percentil 29.8 (SD 26.9). This reflects defective group functioning. The most of the patients' results were in the defective range (64%, under 30 words), some of them in the subnormal (12%, under 40 words), normal (8%, 40-59 words) and some even in the above average range (16%, above 60 words).

The mean total grey matter volume was 779 ml (SD 59.5), the mean total white matter volume was 460 ml (SD 42.2). Voxel-wise simple regression analysis showed significant positive correlation of regional gray matter and VFT score in the posterior part of superior temporal gyrus, on the borders with middle temporal gyrus and inferior parietal lobule (BA 40). As for the regional white matter volume there was one significant cluster in the depth of the inferior frontal gyrus, pars triangularis (BA 45)

Table 1. Positive correlations of regional tissue volumes with VFT scores

MNI coordinates x y z	Area	Number of significant voxels	CNS tissue
-51 -48 20	STG	171	GM
-49 19 27	IFG	119	WM

Legend: This table shows MNI coordinates of local maxima of significant clusters thresholded at the voxel level $p < 0.001$ and the least number of consecutive voxels in a cluster set to 100. STG - superior temporal gyrus, IFG - inferior frontal gyrus, GM - gray matter, WM - white matter.

DISCUSSION

We have found that the ability to generate cued words in the first episode schizophrenia is based on the structural integrity of gray matter of superior temporal gyrus and prefrontal white matter. Previous work has suggested that schizophrenia patients are not able to increase prefrontal activity and to decrease activity in the temporal areas when solving the Verbal fluency task. This was interpreted as an inability of prefrontal cortex to suppress inappropriate words generated in the STG and support the processing of cue-appropriate words. Such a phenomenon was attributed to the fronto-temporal disconnection in schizophrenia (Frith et al., 1995). Our data seems to be in accordance with these findings, adding to the body of knowledge the possibility that such fronto-temporal disconnectivity has a morphological correlate, arising not only from inadequate coupling/synchronization of function between prefrontal and temporal cortex. The data also show the importance of the temporal lobe abnormalities for the ability of schizophrenia patients to solve the VFT.

The limitation of the study is the inability to more generalize the findings due to the absence of data in healthy controls and restrictions of the study sample to the first-episode patients. It might not be considered as a serious problem in the context of the study goal, i.e. to look for the functional correlates of brain morphology changes in the first-episode schizophrenia and to find out the morphological correlates of “fronto-temporal disconnectivity” often seen during the generation of cued words. We can also only deduce the functional importance of the observed correlations since we have no knowledge, whether patients actually used these particular areas during the solving of VFT. The problem might be solved using combination of VBM and functional neuroimaging. The threshold set to 0,001 without the correction for multiple comparisons might yield the results to be false positive. We tend to think this is not the case since we used prior anatomically constrained hypothesis, the results being in accordance with the literature data and physiologically meaningful.

In summary, the study demonstrates that morphology in fronto-temporal areas has functional consequences. Conversely, the ability to solve the verbal fluency task, i.e. the ability to generate context appropriate words, is not only the result of abnormal FT co-operation or ability to “hire” prefrontal activity when necessary, but also stems from the condition of relevant neuronal networks.

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REFERENCES

- Antonova, E., Kumari, V., Morris, R., Halari, R., Anilkumar, A., Mehrotra, R., & Sharma T (2005). The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. *Biological Psychiatry*, 58, 457-467.
- Bonilha, L., Molnar, C., Horner, M.D., Anderson, B., Forster, L., George, M.S., & Nahas, Z (2008). Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. *Schizophrenia Research*, 101, 142-151.
- Frith, C.D., Friston, K.J., Herold, S., et al. (1995). Regional brain activity in schizophrenic patients during the performance of a verbal fluency task. *British Journal of Psychiatry*, 167, 343-349.
- Good, C.D., Johnsrude, I., Ashburner, J., Henson, R.N.A., & Friston, K.J., Frackowiak, R.S.J. (2001). Cerebral Asymmetry and the Effects of Sex and Handedness on Brain Structure: A Voxel-Based Morphometric Analysis of 465 Normal Adult Human Brains. *NeuroImage*, 14, 685-700.
- Honea, R., Crow, T.J., Passingham, D., & Mackay, C.E. (2005). Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal Psychiatry*, 162, 2233-2245.
- Salgado-Pineda, P., Baeza, I., Perez-Gomez, M., Vendrell, P., Junque, C., & Bargallo, N., Bernardo, M. (2003). Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naïve schizophrenic patients. *NeuroImage*, 19, 365-375.