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# Hypofrontality in neuroleptic-naive schizophrenic patients during the Wisconsin Card Sorting Test – a fMRI study

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**Abstract** Functional neuroimaging findings of "hypofrontality" in schizophrenic patients – as tested with the Wisconsin Card Sorting Test (WCST) – are still controversial, mainly due to methodological aspects and the heterogeneity of the patient samples. To measure WCST specific and reproducible reduced cerebral activations in schizophrenic patients, we revised the study design and patient recruitment, respectively. For this purpose, we used an adequate active control task instead of an undefined rest condition to determine exclusively WCST specific cerebral activations. In addition, we focused on the investigation of modified activations between a selected group of neuroleptic-naive schizophrenic patients and carefully matched healthy controls by means of functional magnetic resonance imaging.

The results indicate that neuroleptic-naive schizophrenic patients show reduced activations in the right frontal and left temporal lobe, as well as in the left cerebellum. By utilizing an active control task all unwanted activations are suppressed. Furthermore the influence of different task performances is reduced. The findings are in line with previous PET and SPECT studies and confirm the "hypofrontality" hypothesis. The findings suggest that "hypofrontality" is not caused by neuroleptic medication.

**Key words** Schizophrenia · Neuroleptic-naive · Functional neuroimaging · Hypofrontality · WCST

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## Introduction

To monitor areas of higher cognitive functions by means of neuroimaging investigations, tasks measuring frontal lobe function have gained particular interest, for example the Wisconsin Card Sorting Test (WCST; Milner, 1963, 1971). This test involves different cognitive abilities like 'working memory' and the faculty to adapt behavior based on performance feedback (Marenco et al., 1993). One fundamental part of the WCST is to discover classification principles. Once such a rule has been successfully established, the classification changes unexpectedly, and the subject has to quit the old and to seek out the new grouping principle. Consequently, execution of the WCST activates a complex cerebral network including not only the frontal cortex, but also inferior parietal lobe, visual association cortex, inferior temporal cortex, and cerebellum (Berman et al., 1995).

As expected, the WCST has often been used as stimulus material in functional brain imaging studies on schizophrenic patients. Most investigations applied positron emission tomography (PET) (Wolkin et al., 1992; Berman et al., 1995, Schröder et al., 1995; Ragland et al., 1998) and single photon emission computed tomography (SPECT) (Weinberger et al., 1986; Rubin et al., 1991, 1994; Woods et al., 1992; Kawasaki et al., 1993; Marenco et al., 1993; Catafau et al., 1994; Parellada et al., 1994, 1998) to monitor differences in cerebral activation, whereas our group has utilized functional magnetic resonance imaging (fMRI) (Volz et al., 1997; Mentzel et al., 1998) for this purpose. The findings of these studies can be summarized as follows:

- While performing the WCST, schizophrenic patients show a reduced frontal activation in comparison to healthy controls, especially in the right dorsolateral prefrontal cortex (e. g. Wolkin et al., 1992; Volz et al., 1997) and in the medial frontal gyrus (e. g. Kawasaki et al., 1993; Schroeder et al., 1995). These findings are summarized as "hypofrontality" (Andreasen et al., 1992; Woods, 1992). Especially patients with a promi-

nent negative subsyndrome show "hypofrontality" (e. g. Schroeder et al., 1995), and "hypofrontality" seems to be no long-term effect of neuroleptic treatment (e. g. Andreasen et al., 1992)

- Modified temporal lobe activations in schizophrenic patients are discussed controversially. Catafau et al. (1994) and Parellada et al. (1998) reported on enhanced cerebral blood flow in the left temporal lobe, which may be correlated with positive symptoms, whereas Ragland et al. (1998) detected a reduced temporal activation.
- The cause of hypofrontality is discussed controversially; some groups reported on higher frontal rest activity in schizophrenic patients, so that during the performance of a cognitive task no further increase is possible (see e. g. Catafau et al., 1994; Parellada et al., 1994). In contrast, other studies reject this enhanced baseline activity and reported that cerebral energy consumption in the frontal lobes of schizophrenic patients remains on a low level while performing cognitive tasks (Parellada et al., 1998). But all these studies used an undefined rest condition. They had no control on what the patient did or thought during this time.

As demonstrated, the findings on WCST related cortical activation changes in schizophrenic patients are still controversial. Causes may be the heterogeneity of the patient samples (medication status), different test and evaluation methods, and in particular the undefined rest condition used in most studies. To exclude some of these uncertainties, we investigated WCST specific cerebral activation differences between a selected group of neuroleptic-naive schizophrenic patients and carefully matched healthy controls. In addition – to determine exclusively WCST specific cerebral activations – we used an adequate active control task instead of an undefined rest condition. To receive high anatomical resolution, we performed a functional magnetic resonance imaging study.

We wanted to confirm the following hypotheses: i) the "hypofrontality" is visible in neuroleptic-naive schizophrenic patients and is ii) not based on an undefined rest condition. Even when performing tasks with different cognitive load, schizophrenic patients show a reduced ability to increase frontal cerebral activity.

## Methods

### Stimulation

For standardized cognitive stimulation, a computerized version of the WCST developed by our group was used. This computer program contained a deck of cards according to the WCST standards. Each card is characterized by color, form, and number of symbols (see Fig. 1 a). Thus, the deck of cards can be sorted in 3 different ways: by symbol, number, or color. For administration, the computer deals 4 cards and proceeds to present the participant a further card that must be matched with one of the four reference cards (Fig. 1 a reference cards in the first row, already matched cards in the second row, in this case sorted by number). After each sort, the computer gives a positive or negative feedback according to the correctness of the classification. A computer selected the sort criterion that changes after eight cumulative correct answers. The participant has to find out the new matching rule by trial and error.

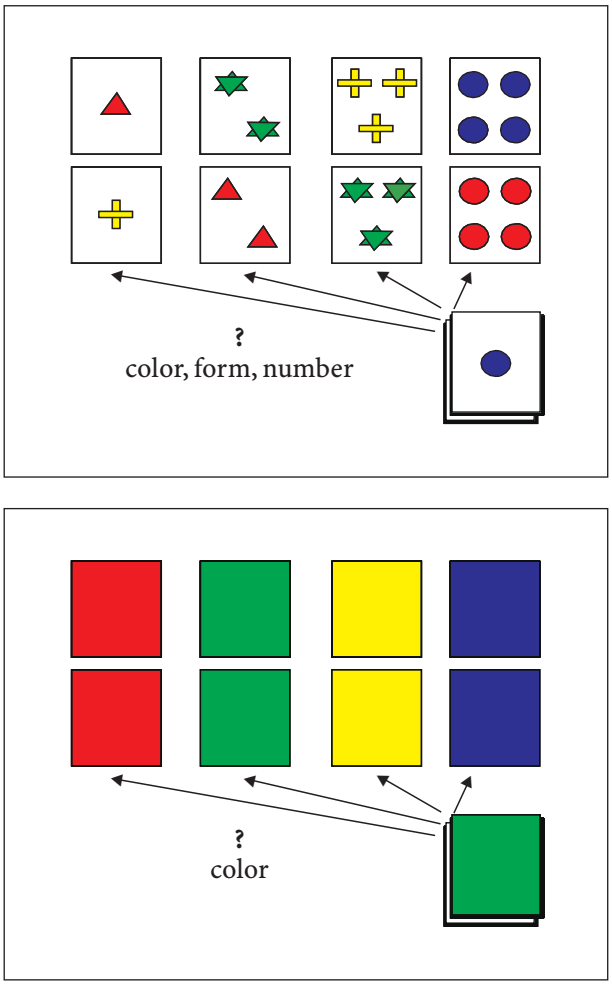


**Fig. 1** Stimulus material: **a** the WCST, **b** the CCST. Details on both tests are given in the text.

As an active control task, we used a colored card-sorting test (CCST, see Fig. 1 b), developed by our group. The test sequence is very similar to the WCST, but the cards are only characterized by color. Accordingly, sorting can only be performed by color. Thus, while performing the CCST the visual stimulus and the required motoric action is the same as when executing the WCST. These unwanted cognitive processes (motor task and visual stimulus) can be suppressed in contrasting WCST versus CCST during evaluation. Higher cognitive processes involved in solving the WCST (working memory and the faculty to adapt behavior based on performance feedback) are not required while performing the CCST and can be extracted using both tasks.

During the fMRI experiment, the stimuli were projected on a screen placed in front of the MRI scanner. The subjects viewed this screen with an angled mirror fixed on top of the head coil. They responded with their right hand using a four-button pneumatic tap-device. The ears of each subject were plugged with wax to reduce effects of scanner noise. A practice session of 10 min was given to all participants prior the fMRI measurement.

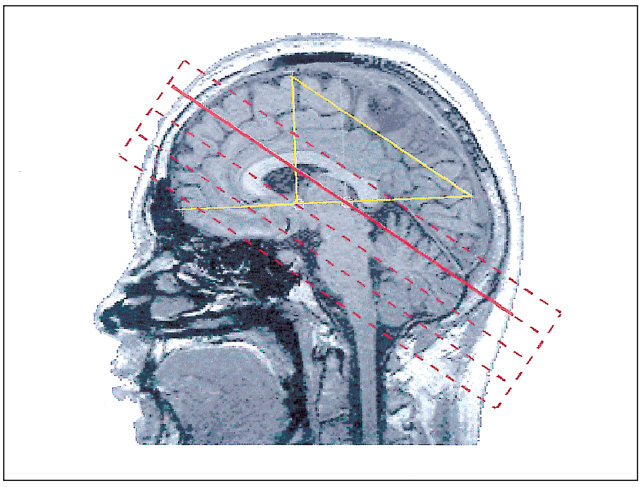

**Fig. 2** Location of the acquired functional MRI images. Four 10 mm slices were sectioned to cover parts of the frontal and temporal lobes, thalamus, hippocampus, and the cerebellum. Slashed lines indicate the 4 slices. The additional lines are utilized for the planning procedure.

### fMRI scanning and evaluation

Imaging was performed on a Gyroscan ACSII scanner (Philips, Hamburg, Germany) at 1.5T using a standard head coil. For functional imaging, a $T_2$*-weighted gradient echo sequence (fast field echo, FFE) was used (TE=50 ms, TR=100 ms, $\alpha$=15°, FOV 230 mm, matrix 128x128). Four 10mm slices were sectioned to cover parts of the frontal and temporal lobes, thalamus, hippocampus, and the cerebellum. The 4 slices are oriented as shown in Fig. 2. The additional lines shown in Fig. 2 are used for the planning procedure (for details, see Volz et al. 1997). Thus, the extent of each voxel was x*y*z = 1.8*1.8*10 $mm^3$. However, no activation data of regions outside these four slices (e. g. in the occipital lobes or the motor cortex) can be obtained.

Initial MRI signal equilibrium was reached by starting with one image at rest. Thus, a series of 55 images (28:25 min) was recorded for each proband. We recorded 6 active epochs with 6 images each, intermitted by rest periods of 3 images each. The two active conditions (WCST and CCST) were randomly distributed over the 6 active epochs, so that each condition was performed 3 times.

Data preprocessing with SPM96 (Wellcome Department of Cognitive Neurology, London) included motion correction (realignment), normalization, and smoothing (in all directions, Gaussian kernel, FWHM 6 mm). Data of all patients and controls showed motion of less than 3 mm or 3° during the whole scanning procedure. For group statistics with SPM96 we applied the random effects model (Holmes and Friston 1998). Thus, the rest period and the two active control tasks were evaluated within one single statistical model. Only significant effects at $p < 0.005$ ($Z > 2.58$, uncorrected) with an extension of at least 10 voxels are considered in the following sections. All images are presented in neurologic orientation (left is left).

**Tab. 1** Education levels

| | Patients | Healthy controls |
|---|---|---|
| School education[1] | 1.78 ± 0.63 | 2.33 ± 0.47 |
| Vocational training[2] | 1.25 ± 0.83 | 2.00 ± 0.76 |

[1] *1* less than 10 years, *2* 10 years, *3* more than 10 years
[2] *0* none, *1* apprenticeship, *2* technical school, *3* university

### Subjects

We included 9 neuroleptic-naive schizophrenic patients (3 women, 6 men, mean age 36.3 ± 10.7 years) and 9 healthy controls, matched for age (mean 36.3 ± 9.9 years) and gender, in the study. Patients and healthy controls showed no significant difference concerning education level (see Table 1). All subjects were right handed as tested with the Edinburgh handedness inventory (Oldfield, 1971). Participants of both groups were free from any internal or neurological symptoms. A history or presence of alcohol or substance abuse was a further exclusion criterion. Drug naivity and the absence of alcohol or substance abuse were secured by blood tests. The healthy volunteers were thoroughly screened for psychiatric illnesses. Persons exhibiting any symptoms or at any family risk factor of psychiatric disorders were excluded. Written informed consent was obtained from both groups. The ethical review board of the University of Jena approved the study.

Patients were diagnosed by two experienced psychiatrists (H. P. V. and S. S.) according to DSM-IV (American Psychiatric Association, 1994). The sample consists of six patients with a paranoid, one with a catatonic, one with a undifferentiated, and one with a residual schizophrenia. The age of onset of the illness was 31.8 ± 10.3 years. Psychiatric symptoms were assessed by the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), the Clinical Global Impression (CGI, National Institute of Mental Health, 1970), and the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) as BPRS = 59.4 ± 9.7, CGI = 5.7 ± 0.5, PANSS (total) = 102.1 ± 15.4, PANSS (negative symptoms) = 25.0 ± 7.3, and PANSS (positive symptoms) = 24.6 ± 7.0.

## Results

### Test performance

Table 2 lines out the test performances of the WCST and the CCST for both healthy controls and schizophrenic patients. Although schizophrenic patients achieved better CCST than WCST results, they showed a poorer performance in all aspects of both tests compared to healthy controls. The most prominent difference is the nearly threefold enhanced response time.

### fMRI results

Comparing the activation differences between the condition WCST and rest periods (Fig. 3), schizophrenic patients show lower activations as controls (see Fig. 4) in the right middle frontal gyrus (BA 9), the left thalamus (anterior nucleus), the right caudate, the corpus callosum, and the left middle frontal gyrus (BA 9).

Contrasting the WCST with the CCST, stronger activations in healthy controls were seen in the right middle frontal gyrus (BA 9, see Fig. 5), whereas no differences

**Tab. 2** Test performance of patients and controls in the WCST and the CCST

| | Number of cards | Relative errors [%] | Completed categories | Response time [ms] |
|---|---|---|---|---|
| *WCST* | | | | |
| Patients | 110 ± 26 | 39 ± 13 | 7.3 ± 4.1 | 3074 ± 1304 |
| Healthy controls | 144 ± 14 | 30 ± 14 | 13.4 ± 2.6 | 1471 ± 400 |
| *CCST* | | | | |
| Patients | 162 ± 20 | 1.7 ± 2.1 | – | 1156 ± 581 |
| Healthy controls | 176 ± 6 | 0.4 ± 0.5 | – | 770 ± 98 |

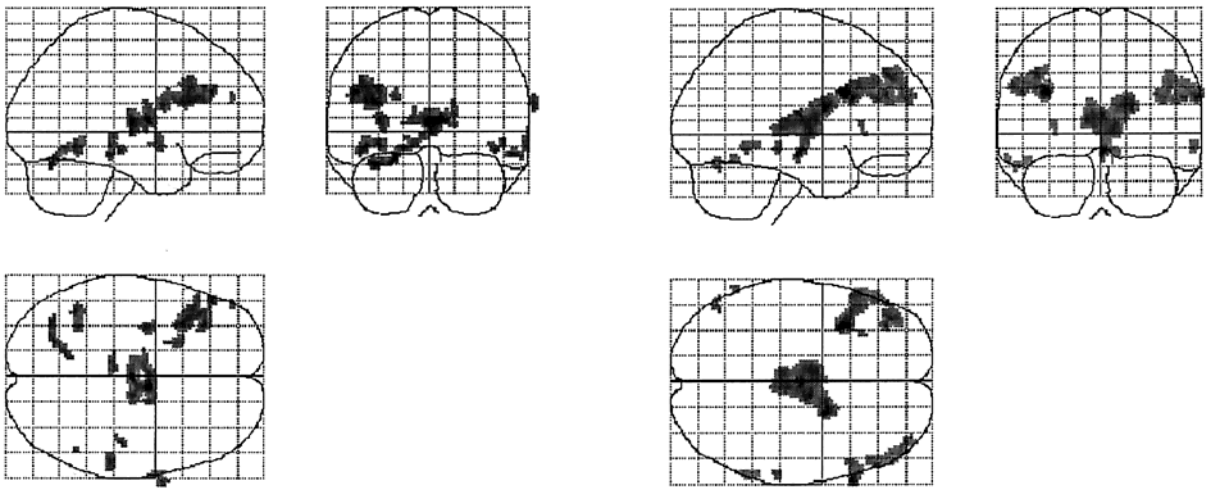

**Fig. 3** Results of the statistical test WCST versus rest, on the left for schizophrenic patients, on the right for healthy controls. Displayed are results with $p < 0.005$ ($Z > 2.58$) and an extend of at least 10 voxels in a so-called glassbrain, which shows the findings in three orthogonal views. All images are presented in neurologic orientation (left is left).

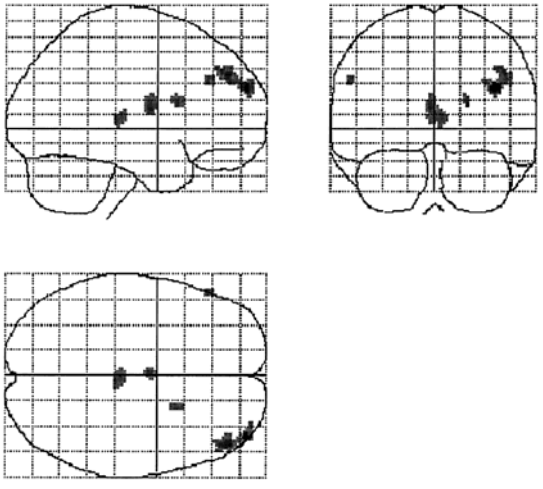

**Fig. 4** Group differences between schizophrenic patients and healthy controls in the activation difference WCST versus rest. The results are presented in the same way as in Fig. 3.

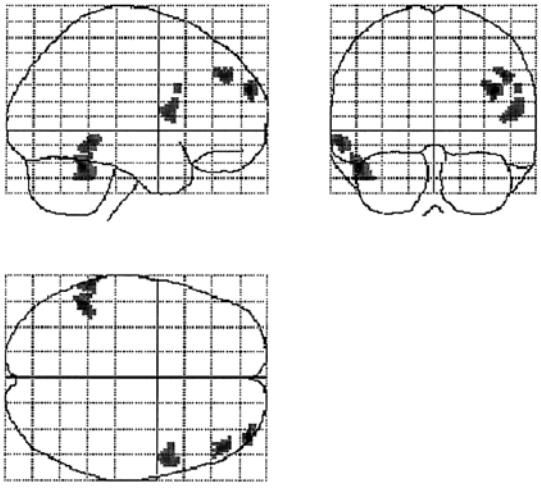

**Fig. 5** Group differences between schizophrenic patients and healthy controls in the activation difference WCST versus CCST. The results are presented in the same way as in Fig. 3 and 4.

were established in caudate, corpus callosum, and thalamus. Distinct activation differences between patients and healthy controls appear in addition to those of **WCST versus rest** in the right precentral gyrus (BA 44), the left middle temporal gyrus (BA 21), and the left cerebellum (cerebellar hemisphere). In all these areas neuroleptic-naive schizophrenic patients show a reduced activation.

## Discussion

The most prominent reductions of WCST specific activations are established in the right middle frontal and precentral gyrus (BA 9 and 44), the left middle temporal gyrus (BA 21), and the left cerebellum of neuroleptic-naive schizophrenic patients as compared to healthy controls. Alterations in caudate, corpus callosum, and thalamus are only present when comparing WCST with rest.

The application of an active control task shows that diminished frontal activations in schizophrenic patients are obviously caused by different cognitive load, because patients show reduced increase of frontal cerebral activity in the more difficult task condition. The diminished activations in caudate, corpus callosum, and thalamus reach significance only for the contrasts task versus rest. They show no dependence on cognitive load and disappeared when comparing WCST and CCST.

The reduced performance of schizophrenic patients in both tests, the WCST and the CCST, has to be considered when interpreting these results. But for a study on unmedicated, acute schizophrenic patients it is not astonishing that the patients fulfill the tests not as good as

controls. The detected activation differences between patients and controls for the contrast WCST versus rest might be explained by reduced performance of the patients. But when looking at the reduced activation of the contrast WCST versus CCST, the dependence on the performance might be diminished. First, for each group the activations of two very similar tasks are compared before the test on group differences is carried out. So only between-task differences in each proband group are considered, which might not depend on the performance as strong as comparisons between a task and rest.

The activation differences in the right frontal and left temporal lobe, which remain when comparing WCST and CCST, agree well with previous findings of PET and SPECT studies (Wolkin et al., 1992; Kawasaki et al., 1993; Schroeder et al., 1995; Ragland et al., 1998) using WCST as stimulus material, as well as with earlier fMRI findings of our group (Volz et al., 1997). The results fit well the "hypofrontality" hypothesis.

Our findings also correspond with studies on volumetric changes in schizophrenic patients (for a current overview, see Lawrie and Abukmeil, 1998). The cerebral structures in which the patients exhibit reduced activations as compared with healthy controls also seem to be smaller in schizophrenics: the frontal gyrus (e. g. Lawrie and Abukmeil, 1998), the temporal lobe (e. g. Barta et al., 1992; Shenton et al., 1992), the thalamus (e. g. Andreasen et al., 1994; Buchsbaum et al., 1996), and the cerebellum (e. g. Gaser et al., 1999; Volz et al., 2000). As the thalamus acts as a central filter for cognitive functions, in the present study activation differences in this structure are only present when comparing task with rest, and not when comparing two tasks differing only in cognitive load.

The involvement of frontal lobe and cerebellum in functional disturbances of schizophrenic patients corresponds with Andreasen's "cognitive dysmetria" model (Andreasen et al., 1998), which assumes a disturbed cortical-subcortical-cerebellar feedback loop as a major cause of schizophrenia. The lack of decreased activations in subcortical regions of schizophrenics when comparing the two tasks WCST and CCST has already been discussed. Reduced thalamic activations become visible only when comparing a task with rest. The additional appearance of functional deficits in the left temporal lobe of all patients may be associated with thought disorders (Barta et al., 1992; Shenton et al., 1992).

Up to now, a few studies have also investigated neuroleptic-free and neuroleptic-naive schizophrenic patients while performing the WCST. Parellada et al. (1994) and Catafau et al. (1994) used SPECT to analyze neuroleptic-naive patients, while Wolkin et al. (1992) and Schröder et al. (1995) utilized PET to examine neuroleptic-free patients. All studies – including the SPECT investigation of Andreasen et al. (1992) that investigated both neuroleptic-naive and neuroleptic-free patients – reported a reduced frontal activation in schizophrenic patients. Thus, our fMRI results well agree with these PET and SPECT findings. We can confirm the hypothesis that "hypofrontality" is visible in neuroleptic-naive schizophrenic patients. "Hypofrontality" is not a pure effect of neuroleptic treatment.

It has to be considered in all points of the discussion that we used a MRI sequence which enables us to detect only 4 subsequent slices, covering the frontal and temporal lobes, thalamus, hippocampus, and the cerebellum. It might well be that above or below these slices activations are considerably different. Since it took about 3 years to complete this study on such a selected patient sample, we had no EPI (echo planar imaging) equipment for the whole period of the study. Thus, it was not possible for us to measure the whole brain within a reasonable imaging time. The number of quite unusual oriented slices was a compromise of a) recording time, b) detection of structures that are considered to show functional disturbances in schizophrenic patients, c) spatial resolution, and d) reproducible planning of the slices.

Taking into account all these issues, we can conclude that the utilization of an active control task provides the extraction of task-specific activations and reduces the influence of different task performances. The fMRI findings on pure WCST specific activation differences between neuroleptic-naive schizophrenic patients and healthy controls correspond well with previous PET and SPECT studies. Our results confirm the "hypofrontality" hypothesis, but we can exclude that "hypofrontality" is a unique effect of neuroleptic medication.

Comparing the results of this study with morphological findings, the areas of reduced cerebral activity in schizophrenic patients seem to exhibit morphological abnormalities as well. Thus, functional and structural abnormalities appear to be connected. But this has to be clarified in a combined functional and morphometric study.

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