Regional brain metabolism as the predictor of performance on the Trail Making Test in schizophrenia. A ^{18}FDG PET covariation study

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Abstract

OBJECTIVES: With the aim to indicate the functional anatomical substrate of cognitive dysfunction in schizophrenia we evaluated the relationship between resting brain metabolism and performance on the Trail Making Test (TMT). As the prerequisite analysis we compared the performance in Part A and B of the TMT between schizophrenic patients and controls. Resting brain metabolism was investigated by ^{18}FDG positron emission tomography (PET) as the probe for the relative regional synaptic strength and density.

METHODS: ^{18}FDG PET data were analyzed by SPM99 with TMT A and B as the covariate ($p \leq 0.001$).

RESULTS: Schizophrenic patients (N=42) had worse performance in both TMT A and B compared to controls (N=42). In schizophrenic subjects ^{18}FDG PET did not predict the performance on Part A (psychomotor speed) but predicted that for Part B (set-shifting and flexibility) of the TMT. The ^{18}FDG uptake in the superior, middle and inferior frontal gyruses bilaterally was associated with better performance in the TMT B. The negative covariation between ^{18}FDG uptake and time spent in the TMT B was detected in the temporal and parietal cortices, pre- and postcentral gyruses, precuneus limbic regions (anterior cingulate, uncus) and the pons.

CONCLUSIONS: Our data indicate that hypometabolism in the frontal lobes and hypermetabolism in the temporo-parieto-limbic regions is the neurobiological basis for deficient TMT B performance in schizophrenia.

ORIGINAL ARTICLE

Introduction

Schizophrenia is a severe neuropsychiatric disorder expressed by positive and negative symptoms, and cognitive dysfunction. Cognitive dysfunction is the characteristic trait marker of schizophrenia and includes deficits of several neuropsychological domains such as psychomotor speed, attention, working memory and executive functions, as well as deficits in controlled attention or planning [1–4].

Neuroimaging studies document that cognitive functioning in schizophrenia is supposed to be closely related to primary brain dysfunction. These studies have consistently produced support for structural changes and decreased metabolism or perfusion in the regions involved in cognitive processing such as in the frontal lobes [5–7], temporal and limbic structures [8–12;57;58], parietal cortex [13–15], cerebellum [16] and basal ganglia [17].

The activation studies evaluating the brain activity during specific cognitive tasks consistently found the deficits in the prefrontal cortex of schizophrenic patients [8;18;19;19–22;22–24]. Although the dysfunction of the prefrontal cortex and other interrelated regions is supposed to be the underlying neurobiology of cognitive dysfunction in schizophrenia [25–27] the functional anatomical substrate of cognitive dysfunction is not well established.

By using ^{18}fluoro-deoxyglucose (^{18}FDG) positron emission tomography (PET) in our study we focused on the functional morphological substrate of the performance on the Trail Making Test (TMT) in schizophrenia. The Trail Making Test (TMT) emphasizes set-switching and problem-solving abilities and demonstrates the ability to alternate between cognitive categories for visual search and sequencing. Comprised of two parts, in Part A (TMT A) subjects are required to rapidly connect a series of 25 circles containing numbers in an ascending order. Part B (TMT B) is more complex than A because it requires the subject to connect numbers and letters in an alternating pattern (1-A-2-B-3-C, etc.) in the minimum time possible [28]. In this way, the TMT provides tasks that demand attention, working memory, concentration and cognitive flexibility (or set-shifting) and planning. Concretely, rapid performance in Part A depends primarily on visual scanning and psychomotor speed. In contrast, in Part B the alternating between two sequences is thought to require executive control, specifically flexibility of thinking and a greater demand for working memory and some authors interpret it as an executive task [29]. Deficits on the TMT have been widely documented for schizophrenics [30–33]. Studies have also found that relatives of schizophrenic patients performed significantly worse than controls on the TMT B with a trend for poorer performance on TMT A [31;34]. The verbal version of the TMT has proven to activate the dorsolateral and medial prefrontal cortices as well as the intraparietal sulci [35]. These clinical and experimental data are in congruence with the hypothetical prefrontal deficit in schizophrenia.

As the prerequisite analysis, we compared the performance on the TMT A and B between our group of schizophrenic patients (N=42) and the 42 control subjects. The primary aim of the study was to detect the relationship between performance on the TMT in schizophrenia and the resting regional brain metabolism measured by ^{18}FDG PET. The use of ^{18}FDG PET in the resting state primarily reflects the regional glutamate turnover at the synaptic level and so ^{18}FDG PET is a probe for relative synaptic strength and consequent functional and metabolic activity of the brain regions [36;37]. Based on neuroimaging and clinical studies that reveal abnormalities in the prefrontal cortex and decreased frontal activation in cognitive tasks negatively affecting cognitive function in schizophrenia patients, we propose that the resting metabolism in the frontal lobes will provide a predictor of performance on the TMT test based on its demand for those cortical areas.

Materials and Methods

Samples. We investigated 42 right-handed subjects with schizophrenia diagnosed according ICD 10, aged 18–55 years [22 men and 20 woman, mean age 24.3, s.d.=9.2) by ^{18}FDG PET and the Trail Making Test. The demographic characteristics are in **Table 1.** Patients were recruited from the Prague Psychiatric Center. With respect to the clinical intention of the institution and the study protocol, the population was relatively undeteriorated with few hospitalizations (mean 2.6, s.d.=2.4) and the study was focused on non-chronic schizophrenic patients. The clinical symptoms were measured by the Positive and Negative Symptom Scale, PANSS [38]. All subjects were mild to moderately ill with a total PANSS mean score of 61.2, s.d.=18.4 (**Table 2**). 37 patients were on antipsychotic drugs prescribed in usual doses. From this group 14 patients used risperidone, 4 quetiapine, 6 olanzapine, 2 flufenazine, 3 clozapine, 1 sulpiride, 3 haloperidol, 1 perfenazine and 1 oxyprothepine. Benzodiazepines were allowed and 7 patients used anticholinergics for exrapyramidal side effects. 5 patients were without antipsychotic medication, 4 of them finished the maintenance treatment from 9 to 148 days before entering the study and 1 was drug naive.

The control sample consists of 42 people (20 men and 22 woman, mean age 29,7, s.d.=11.6) from a normal population. All of the subjects in both the schizophrenic and control groups were of Caucasian origin. Applicants with significant medical problems, a history of head trauma, and alcohol or drug abuse within the last 6 months were excluded. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the written informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The local ethics committee approved the study.

Table 1: The demographic characteristics and performance on the Trail Making Test Part A (TMT A) and Part B (TMT B). **Note:** "±" means s.d. and "*" indicates p≤0.001.

	Controls	Schizophrenics
N (males:females)	42 (20:22)	42 (22:20)
Age (years)	29.7 (±11.6)	24.3 (±9.2)
Education level (1–3)	2.06 (±0.18)	1.96 (±0.5)
SCH duration (months)	–	46.6 (± 58.8)
Number of hospitalizations	–	2,6 (±2.4)
TMT A (sec.)	28.2 (±6.9)	**43.0 (±14.7)***
TMT B (sec.)	64.1 (±21.6)	**105.4 (±45.0)***

Table 2: The description of the symptomatology in the schizophrenic group measured by the the Positive and Negative Symptom Scale (PANSS) for positive (PANSS P), negative (PANSS N), global (PANSS G) and total (PANSS tot) symptoms.

	Mean	s.d.	Min.	Max.
PANSS P	14.6	5.5	6	29
PANSS N	16.5	6.4	7	31
PANSS G	33.5	9.4	16	57
PANSS tot.	64.6	18.6	30	108

Experimental procedure and PET investigation. Patients performed TMT A and B testing within 4 days of the PET imaging, for which they were fasted for at least 6 hours before. In a dimly-lit and quiet room, 3 MBq/kg of ^{18}FDG was administered via a peripheral vein catheter. The patients rested for 30 min. in the same room, and then a 2D "hot" transmission scan of the brain was performed, lasting between 5 and 10 minutes (transmission scanning time was corrected to allow for decay of the transmission sources). The data were acquired using the ECAT EXACT 922 (CTI/Siemens, Knoxville, TN) PET scanner. The scan was immediately followed by 3D emission scanning which lasted 15 minutes. The data acquired were reconstructed by iterative OS-EM algorithm (matrix: 1282, brain mode, 47 slices, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) and implemented using ECAT 7.2 software.

PET data analysis and statistics. The data analysis was performed using Statistical Parametric Mapping, SPM99 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks, USA). The PET scans were converted into the Analyze format, interpolated from 47 to 68 slices, normalized into standard stereotactic space by the use of bilinear sinc. Interpolation and smoothed with an isotropic Gaussian filter (full width at half maximum of 12 mm). The global intensity differences were corrected by proportional scaling (global mean to 50, analysis threshold 0.8) and global calculation was performed by the mean voxel value. The data-preprocessing procedure resulted in the generation of a spatially normalized image of ^{18}FDG uptake for every voxel in 68 horizontal slices through the brain. A covariate analysis was used to determine the negative and positive co-variation between time spent in TMT A and B, and the PET ^{18}FDG uptake. Statistical parametric maps of T-values were created and the anatomical locations of the activated areas were determined in the normalized space. The p-values at voxel-level were ≤0.001. Chi square was used to determine the differences in the predicted voxels in the left and right hemispheres.

Descriptive statistics were applied to all of the demographic variables. Because the psychopathological and neuropsychological measures were normally distributed (Wilks Shapiro test) the relationship between TMT A and B and age, PANSS, education and duration of schizophrenia were analyzed by Pearson correlation coefficient. Between groups comparisons of demographic data and TMT were performed using t-tests. Due to the different number of patients in the drug free group versus to the patients using antipsychotics we used the nonparametric Mann Whitney test for the comparison. P-values of 5% or less were considered statistically significant.

Results

The group of schizophrenic patients and controls did not differ in age, education status or the males/females ratio (**Table 1**). The schizophrenic patients had a worse performance on the TMT compared with the controls in both Part A and Part B (p≤0.001).

When evaluating the influence of age, PANSS subscores, duration of schizophrenia, education or gender on performance in TMT A and TMT B we found only a positive correlation between TMT A and the PANSS global and total scores (p≤0.05 for both). Other analyses were not significant. We did not detect significant differences between patients with current antipsychotic treatment and the drug free subgroup in both the TMT

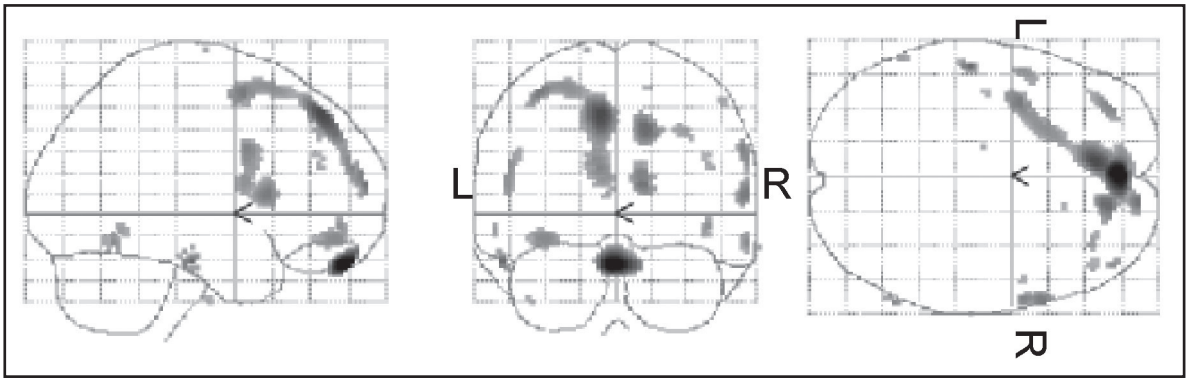

Figure 1: Negative covariation of performance on the TMT B (time) and ^{18}FDG uptake PET in the schizophrenic sample. For technical details and a list of all significant changes, see Table 2. Note: R, right hemisphere; L, left hemisphere.

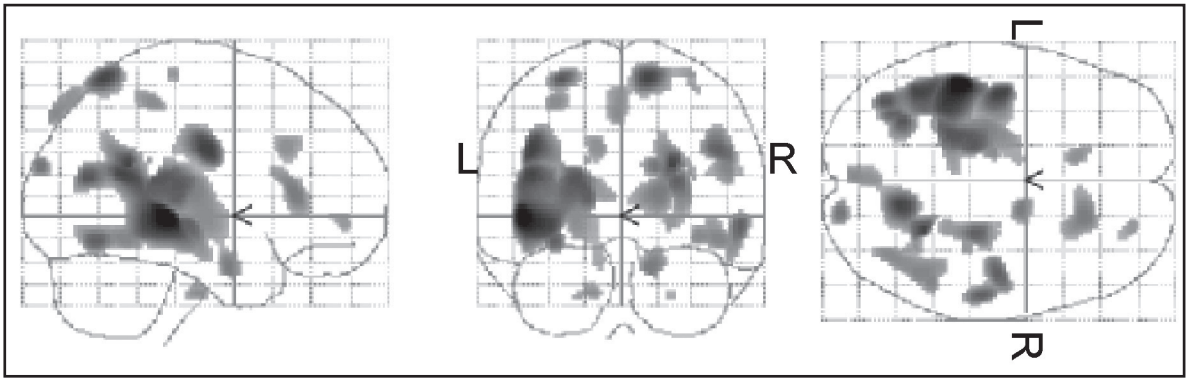

Figure 2: Positive covariation of performance on the TMT B (time) and ^{18}FDG uptake PET in the schizophrenic sample. For technical details and a list of all significant changes, see Table 2. Note: R, right hemisphere; L, left hemisphere.

A (mean = 43.2, s.d.= 15.1 vs mean = 41.4, s.d.=12.8) and TMT B (mean = 108.5, s.d.=47.3 vs mean = 86.6, s.d.=20.3).

Evaluation of the relationship between resting brain metabolism and TMT performance did not yield any covariation between the TMT A and ^{18}FDG uptake.

However, in the more complex TMT B subtest we found a negative covariation of time spent to complete it with metabolic activity in the superior, middle and inferior frontal gyruses bilaterally ($p \leq 0.001$, **Table 3, Figure 1**). This finding indicates that the higher the metabolism is in these regions the better is the cognitive performance on the TMT B. Moreover the number of voxels over the threshold was higher in the left hemisphere in comparison to the right one (595 vs. 235, chi square=155.9, $p \leq 0.0001$) and metabolism in the left prefrontal cortex is a stronger predictor of the cognitive outcome in the TMT B subtest.

Using the opposite contrast, the negative covariation between brain metabolism and time in TMT B performance was found in the temporal, parietal cortex, pre- and postcentral gyruses, precuneus limbic regions (anterior cingulate, uncus), and pons. (**Table 3, Figure 2**). These findings indicate that the higher the metabolism is in these regions the worse is the performance on the TMT B. The number of voxels over the threshold was again higher in the left hemisphere in comparison to the right one (4299 vs. 2238, chi square=671,9, $p \leq 0.0001$).

Discussion

In our sample we confirmed that patients with schizophrenia have worse cognitive performance on both subtests of the TMT compared with the control group. These data are consistent with previous findings that patients with schizophrenia performed poorly on this test in comparison to the healthy subjects [39;40;52]. The inability to effectively plan, in addition to longer fixation and insufficient sequencing of planning and acting was proven as the core neuropsychological substrate for the deficit of the TMT in schizophrenia [52]. The same authors also did not find a relationship between the «planning variables» with psychopathology, course of illness or antipsychotic medication [41;42;52]. However, two studies [43;44] found that the deficit in the TMT B is more pronounced in disorganized patients. Other studies examining the effects of medication on either the TMT A or B found no significant effect of antipsychotic treatment [45–48] with the exception of one analysis of higher doses of classical neuroleptics [49]. Consistently, in our sample the clinical and demographical variables did not influence the TMT performance with the exception of a correlation between the PANSS global and total scores and the TMT A (a possible effect of lacking concentration in this easier part). Taken together, our data and the majority of previous studies confirm that the deficit in TMT appears to be a trait-like characteristic marker of

Table 3: Positive and negative covariation between time spent in the Trail Making Test B, and the PET ^{18}FDG uptake. The p-values for voxels exceeding the height threshold T=3.29 and are lower than 0.001. The extent threshold is ≤9 voxels.

Ke	x,y,z	R or L	Gyrus	Brodmann area
positive covariation				
4007	–46 –32 0	L	Middle Temporal Gyrus	21
	–42 –14 32	L	Precentral Gyrus	6
	–42 –52 20	L	Superior Temporal Gyrus	22
440	12 –62 64	R	Precuneus	7
	–2 –84 48	L	Precuneus	7
	–2 –78 54	L	Precuneus	7
216	24 –50 24	R	Cingulate Gyrus	31
	32 –54 20	R	Middle Temporal Gyrus	39
119	–28 –60 64	L	Superior Parietal Lobule	7
198	56 –22 –4	R	Middle Temporal Gyrus	21
321	26 –24 16	R	Claustrum	*
	24 –38 14	R	Caudate Tail	
191	46 –14 30	R	Precentral Gyrus	6
54	16 –92 24	R	Cuneus	19
87	14 –2 –24	R	Uncus	28
265	18 28 10	R	White matter	
319	46 –50 –10	R	Fusiform Gyrus	37
	36 –68 –10	R	Fusiform Gyrus	19
79	50 –46 22	R	Inferior Parietal Lobule	40
36	–14 –18 –36	L	Pons	
69	–30 –40 54	L	Inferior Parietal Lobule	40
68	–12 24 32	L	Cingulate Gyrus	32
19	32 –30 66	R	Postcentral Gyrus	3
25	22 52 –2	R	Superior Frontal Gyrus	10
14	34 –58 60	R	Superior Parietal Lobule	7
10	56 –26 22	R	Postcentral Gyrus	40
negative covariation				
165	–2 54 –24	L	Superior Frontal Gyrus	11
353	–6 42 48	L	Superior Frontal Gyrus	8
	–36 4 58	L	Middle Frontal Gyrus	6
	–8 56 22	L	Superior Frontal Gyrus	9
79	14 48 40	R	Superior Frontal Gyrus	8
40	14 62 14	R	Superior Frontal Gyrus	10
57	62 16 10	R	Inferior Frontal Gyrus	44
38	60 6 30	R	Precentral Gyrus	6
39	–34 48 –12	L	Superior Frontal Gyrus	11
12	62 –58 –14	R	Inferior Temporal Gyrus	20
38	–52 6 16	L	Inferior Frontal Gyrus	44
	–50 8 24	L	Inferior Frontal Gyrus	9
9	32 40 40	R	Middle Frontal Gyrus	8

Note: R, right hemisphere; L, left hemisphere; x, y, z, the coordinates of the Talairach space for each maximum; Ke, is the number of voxels in the cluster.

schizophrenia and the clinical measures and antipsychotics have no or very little effect on performance on the TMT.

In our study we evaluated the relationship between the TMT performance and the resting brain metabolism. Hence, our neuroimaging data did not answer the question of which brain areas are activated by the test but they answer the question whether the resting metabolism predicts the neurocognitive performance. The specified resting condition was described as Random Episodic Silent Thinking (REST) and was proven to offer favorable reliability in PET findings in a schizophrenic population [50]. The ^{18}FDG PET uptake in the resting state primarily reflects the regional glutamate turnover at

the synaptic level and so ^{18}FDG PET is the probe for synaptic strength, and local integrated synaptic activity and integrity [36;51]. The physiological relevance of ^{18}FDG uptake was recently documented directly by the correlation with synaptophysin level in baboons and is accepted as the marker of synaptic density[37]. Therefore, in our study the ^{18}FDG uptake is used to indicate the synaptic density as the substrate for effective cognitive functioning in TMT A and B.

We did not find any relationship between the performance on the Part A of the TMT and the ^{18}FDG PET uptake. This negative finding is in congruence with the studies demonstrating that TMT A in contrast to TMT B did not discriminate schizophrenic and control subjects [39;40;52]. The TMT A is a simple task mostly reflecting psychomotor speed, and it does not involve set-switching abilities or executive functions.

However, robust findings were detected in TMT part B for both positive and negative prediction by PET. We found that the higher the metabolism was in the frontal lobes, the shorter was the time of TMT B performance. This observation supports the hypothesis that deficit in prefrontal lobe neurodevelopment leads to cognitive dysfunction in schizophrenia [24–27]. These findings are in congruence with our a priori formulated hypothesis and the p-level 0.001 uncorrected for multiple comparisons is fully acceptable [53].

The negative covariation between ^{18}FDG uptake and time spent in the TMT B were detected in the temporal and other neocortical and limbic regions (anterior cingulate, uncus) and pons. Generally, the clusters predicting the negative cognitive performance on the TMT B are localized more posterior than regions predicting good performance. These regions were not involved in the a priori hypothesis and due to the lack of correction for multiple comparisons the results should be interpreted cautiously. The disturbances in the identified regions were previously documented in schizophrenia and in most studies they were associated with positive symptoms. The differences in metabolism or perfusion were documented for temporal and limbic lobe [11;12;53–56], anterior cingulate [57;58], and hippocampus [9–10;53;57;59]. The superior parietal cortex was also found to be overactive in relation to positive and disorganized symptoms [13–15]. In the context of these observations, it is possible to speculate that the regions, which covary with a longer time in the TMT B, reflect the positive and disorganized dimensions of schizophrenia.

In our study we found significant lateralization in favor of the left side in both the positive and negative covariation with the TMT B. This finding would be interpreted both as the lateralization of the TMT B task [35] and as the asymmetrical (left sided) distribution of brain dysfunction in schizophrenia documented by several neuroimaging studies [60–66].

In conclusion, in our study the prefrontal activity is a clinically positive predictor of better TMT B performance and temporal, limbic and parietal hyperactivity is the negative predictor of TMT B performance. The core distinction between prefrontal and more posterior regions in the opposite direction for prediction of TMT B performance is congruent with the neurodevelopemental disconnection theory of schizophrenia. This concept refers to the failure of proper integration (disconnection) between the prefrontal and temporal cortices. The attenuation of fronto-temporal integration results in the hypoactivity of the prefrontal cortex and hyperactivity of the temporal cortex and other interconnected regions in tasks that require the activity of the prefrontal cortex [67–74]. In the resting state the relatively higher activity of the temporal cortex should be expected as a response to decreased inhibition of the prefrontal cortex [24;75]. This dysfunction within a widely distributed neocortical-limbic neural network would result in failure of cognitive functions such as planning ability as detected by the TMT B.

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