Influence of working memory load on brain activation patterns in schizophrenia. Preliminary results of a multivariate fMRI study.

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Introduction

Cognitive and especially working memory deficits are regarded as a core symptom of schizophrenia. It is not yet clear though, on what neurobiological dysfunction this deficit is based. Since there is evidence that in schizophrenia cerebral connectivity is disturbed, we used a multivariate method to examine functional connectivity during a working memory task in schizophrenic patients.

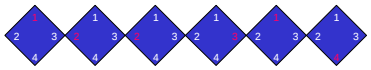
Methods

subjects:
11 DSM-IV schizophrenic patients of our clinic and 11 healthy controls.
All right handed. Written informed consent.

	patients	controls	p (t-test)
age (years)	29.0 (+/-7.7)	28.7 (+/-9.8)	0.940
school education (years)	12.1 (+/-1.6)	11.7 (+/-1.8)	0.619
gender	7 male	7 male	-

medication:
7 risperidone, 3 quetiapine, 2 clozapine (one patient had risperidone and quetiapine)

task:



answer:	**0-back:**	1	2	2	3	1	4
	1-back:	-	1	2	2	3	1
	2-back:	-	-	1	2	2	3

design:
blocked design, 7 blocks with 3 conditions: 0-back, 1-back, 2-back. fixed sequence. Each condition: 11 stimuli à 0.5 sec, block duration 21 sec. interstimulus interval ~1.86 sec. Rest = 5 sec instruction+1 sec blank screen between all tasks.

scanning parameters:
1,5 T GE Signa Scanner; echo planar imaging, TR 3000 ms, TE 50 ms, flip angle 90°, bandwidth 62 kHz, 28 slices à 5mm, interleaved, FOV 24x24cm, matrix 64x64 voxels.

data analysis:
preprocessing
(SPM2:www.fil.ion.ucl.ac.uk):
slice time correction, realignment, normalising (voxel size 3x3x3mm), smoothing (kernel=7mm);
group analysis: subjects = data extension in time domain. Therefore first-level fixed model analysis in SPM2 with subjects not defined as sessions, but as regressors in the model (see fig.1).
Multivariate analysis: Multivariate Linear Model of the MM-toolbox by F.Kherif and J.-B.Poline (http://www.madic.org):
1) reduction of the data by projection on the space defined by the model (F-contrast of task-regressors).
2) computation of 3 eigenimages that are correlated with linear combinations of the task regressors.

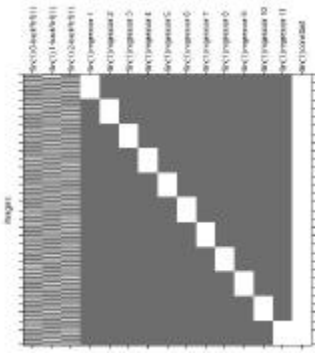


figure1: *SPM design matrix for 11 subjects, first level fixed model*

Discussion

The presented multivariate method can be a useful tool to examine differences in cerebral networks activated by specific tasks.
The 3 eigenimages that were generated correlated with theoretically meaningful combinations of the regressors and represent networks of activation that are known from the literature (e.g. frontoparietal network of the second eigenimage).
An interesting finding was the fact that the most prominent network of activation was more active during the one- than the two-back task in schizophrenic patients and vice versa in controls. This is in line with the idea of an inverted U-shape connection between n-back load and cerebral activation that is shifted to the left in the case of schizophrenia [1]. An alternative explanation is the use of a different strategy in the one-back task in patients [2], which is supported by differences in the eigenimages.
A major problem of the method is the fact that there is no statistical evaluation. So the findings are purely descriptive and cannot be generalised.

Results

behavioural results:

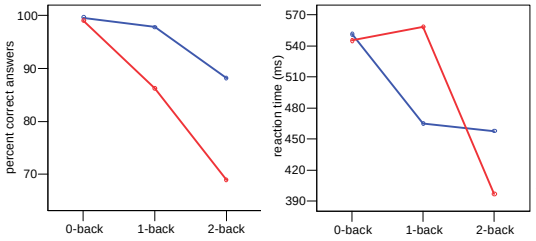


fig.2 *left: percentage of correct answers right: reaction times for the correct answers. group means blue=controls, red= patients*

% correct answers: ANOVA: task: p=.002; group=.007; task x group: p=.064.
reaction times: ANOVA: task: p=.002; group: p=.898; task x group: p=.064

results of the multivariate fMRI analyses:
1) whole sample (N=22):

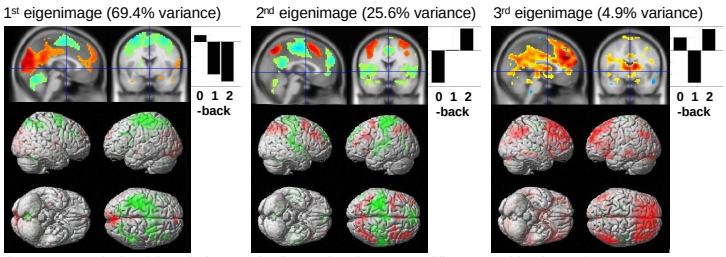


fig.3 *MLM analysis of the whole sample. first 3 eigenimages and linear combinations of regressors.*

1st eigenimage	2nd eigenimage	3rd eigenimage
(increasing wm-load)	(2-back vs 0-back):	(0- and 2-back vs 1-back)
L post- and precentral gyrus	R+L DLPFC	R+L prefrontal medial gyrus
R cerebellum	R+L premotor areas	anterior cingulate gyrus
R>L inferior parieatl cortex	R+L inferior parietal gyrus	R+L caudate
R>L DLPFC	SMA	R thalamus
L insula	R+L insula	R DLPFC
SMA	negative:	R+L inferior parietal gyrus
R>L premotor regions	L+R post- and precentral	R+L middle temporal gyrus
negative: cuneus	prefrontal medial cortex	negative: no activation
R+L lingual gyrus	R+L sup. temporal gyrus	
medial prefrontal cortex	posterior cingulate	
ant. and post. cingulate	R cerebellum	

2) 1st eigenimage, separate analyses (N=11):

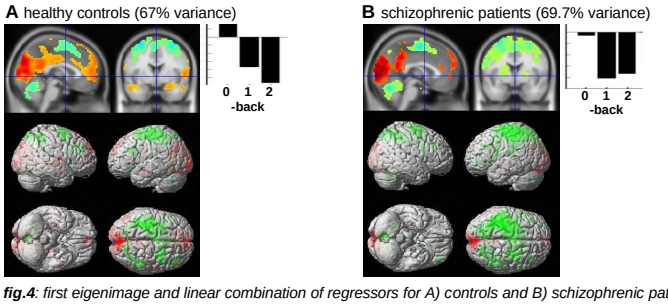


fig.4*: first eigenimage and linear combination of regressors for A) controls and B) schizophrenic patients.*

regressors:
controls=increasing wm-load
patients=more pronounced one-back, zero-back in same direction
eigenimages:
controls: activation during wm-tasks in L pre- and postcentral gyrus, R+L premotor areas, R cerebellum, SMA, R>L DLPF and inferior parietal cortex, R>L inferior frontal gyrus. Deactivation in cuneus, R+L lingual gyrus, medial prefrontal area, cingulate gyrus, R+L parahippocampal gyrus.
patients: activation in R>L striatum, no deactivation in parahippocampal gyrus

References

1) Manoach D. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res 2003; 60:285-298.
2) Krieger et al. Executive Function and Cognitive Subprocesses in First-Episode, Drug-Naive Schizophrenia: An Analysis of N-Back Performance. Am J Psychiatry 2005:162:1206-1208.

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