Modulation of Working Memory and Visual Information Load in Schizophrenic Patients and Healthy Controls: Preliminary Results

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Purposes

There is ample evidence that schizophrenia is associated with cognitive deficits, particularly in the domains of attention, working memory and executive functions. A model of cortical inefficiency has recently been proposed by Manoach (Schizophr. Res 2003 (60) 285-98) and suggests an inverted U-shape of BOLD activation intensity with increasing working memory/executive function demand. This curve appears to be shifted in schizophrenic patients relative to normal controls in terms of an earlier increase. In contrary, with executive function/working memory demand exceeding capacity, an earlier decrease of the response is also seen. The goal of the present study is to examine the predictions based on this model and the possible therapeutic modulation of the results.

Schizophrenic patients also have well-known deficits in selective visual information processing. It is however unclear, if the mechanism of selective attention for perception is affected due to deficits in top-down or bottom-up regulation. By parametrical modulation of working memory load and competing irrelevant stimuli, the present study was designed to additionally address this question.

The presented material covers behavioural data from a pilot study testing a novel fMRI-paradigm as well as first results from healthy controls performing the paradigm in the scanner.

Methods

Well characterized neuropsychological paradigms (n-back) covering attention, executive functions as well as working memory under different load conditions were adopted for use in the magnet. Combining 1-back and 2-back tasks in pseudorandomized order with background images containing a parametric defined degree of noise, an fMRI-paradigm in block design could be established. Pictures were controlled for minimal arousal and neutral emotional valence (IAPS):

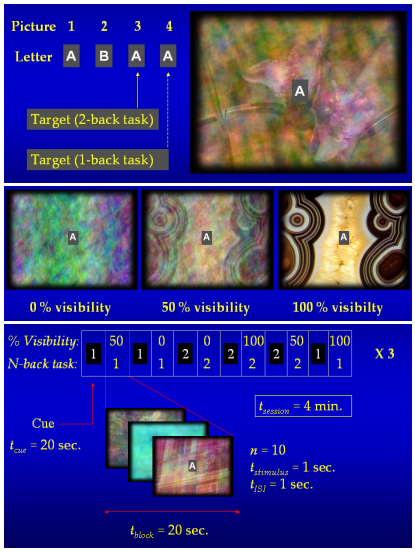

Fig. 1: Experimental Design.

a) N-back working memory task. 1-back and 2-back tasks had to be performed. Letters/colours served as stimuli and were presented in front of a background picture.

b) Background picture visibilty. Object pictures of neutral emotional value with little effect on arousal (IAPS) containing a defined degree of noise were used as distractor.

c) Functional MRI paradigm. Three subsequent sessions were performed in the scanner, each consisting of a pseudo-randomized series of tasks with different n-back level and background object image visibility. Each task was preceded by a cue indicating n-back level.

A neuropsychological pilot study using this paradigm was performed with 12 male right-handed inpatients (UKE Hamburg) and 12 healthy controls matched for age, sex and educational level. Patients were clinically characterized (PANSS, BPRS, CGI, GAF), all probands completed the fMRI-paradigm as well as a set of neuropsychological tests covering the domains of interest.

Single healthy probands also performed the paradigm in the scanner. Data acquisition was carried out using an EPI T2* sensitive sequence (40 contiguous axial slices, 3 mm thickness, TR 2.5 s, TE 25 ms, flip angle 70°, FOV 192 x 192 mm², matrix 64 x 64) in a 3 Tesla MRI-scanner (Siemens Trio). SPM2 was used for data analysis.

Results/Discussion

Patients (mean age 32.6 years, SD 9.1 years) recruited from the psychiatric ward were subacutely ill (mean global PANSS score of 62.3, SD 10.8; mean BPRS score of 39.5, SD 7.0; mean CGI-S score of 4.0, SD 0.7). Most of them received medical therapy using an atiypcal antipsychotic treatment (amisulpride [n=2], olanzapine [n=4], risperidone [n=2], ziprasidone [n=1]), one patient was on neuroleptic treatment with pimozide. Data from the pilot study could show significant differences in performance between patients and controls:

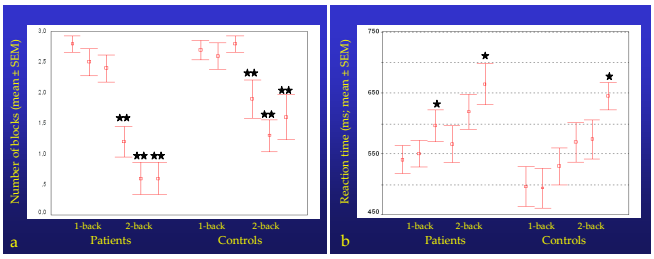

Fig. 2: Pilot study results. *a) Correctly answered blocks.* Number of correctly answered blocks for 0%, 50% and 100% visibility of background object images (left to right) for patients and controls. *b) Reaction times.* N-back reaction times for 0%, 50% and 100% visibility of background images (left to right). An asterisk indicates a significant difference from the corresponding n-back value for 0% visibility (paired samples t-test, $p < 0.05$). Two asterisks indicate a significant difference of the values from the 1-back value with corresponding visibility (paired samples t-test, $p < 0.01$).

Reaction times as well as error rates in both groups depended significantly on task difficulty, i.e. n-back level and distractor visibility. A successful modulation of performance by working memory load and visibility could be shown.

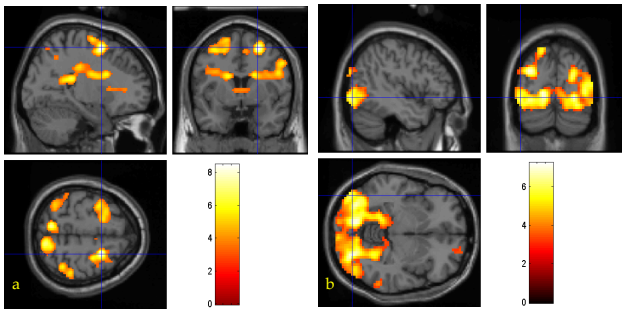

Fig. 3: Single case fMRI analysis for the paradigm using colours as stimuli. *a) Contrast for 2-back vs. 1-back.* Activation of several areas previously associated with working memory, e.g. the dorsolateral prefrontal cortex, is seen. *b) Contrast for 100% visibility vs. 0% visibility.* Areas involved with background object image processing are activated, especially the bilateral lateral occipital complex ($p < 0.001$ uncorrected).

As expected, single case analysis of fMRI data demonstrates the activation of the working memory and attention network depending on task difficulty. Because the processing of visually presented letters is also known to cause activation of the lateral occipital complex as seen in our case, we performed the paradigm described above using colours as stimuli instead of letters. Figure 3b shows that the activation of the bilateral lateral occipital complex depending on background image visibility remained detectable using the modified paradigm.

Conclusion

These results show for the first time the applicability of the chosen paradigm (using colours as stimuli instead of letters) for use in imaging studies. Furthermore, they indicate the ability of said paradigm to identify neural correlates of cognitive dysfunction in schizophrenia.

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