Indication for reduced neuro-functional reserve and connectivity in patients with subcortical vascular encephalopathy

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Introduction

Subcortical white matter changes and disconnection are the pathological substrates in patients with microvascular parenchymal lesions. Such tissue changes occur with age and in association with risk factors for small vessel disease (diabetes, smoking, hypertension, hyperhomocysteinemia). The common clinical features are slowing and apraxia of locomotion and short term memory disturbances. As these clinical features show slow progression commonly without a stroke-like dynamic, they are often neglected and considered as age effects. In particular the early and subtle features, at oligo- or asymptomatic stages are poorly understood. In this study, we investigated patients with clinically mild forms of subcortical vascular encephalopathy (SVE) in regard to their short memory brain activity.

Methods

25 subjects (10 female, 66±9 a) with mild symptoms of SVE and controls were recruited and participated in this study. Written informed consent was provided before examination and the study was approved by the local ethical committee. The subjects performed three different tasks: 1.) an "alertness" task, 2.) a "zero-back" attention task and 3.) a "two-back" working memory task. During the "alertness" task, the number "2" was presented in pseudo-randomized intervals between 1.2 and 2.8s. Subjects were asked to respond as fast as possible by pressing the button on a response device. In a 36s interval, the number "2" appeared 18 times. In the "zero-back" task, random numbers from 1-9 were presented. Subjects had to press the button, if the number "2" was displayed. In one task block, 18 numbers appeared in intervals of 2s. Finally, in the "two-back" task, the numbers were presented in the same way as in "zero-back". Response was requested, if a number was repeated which was presented two steps before. The cognitive tasks were administered using IFIS-SA (MRI Devices, Waukesha, USA) during functional scanning. Performance was controlled visually by a response monitor unit.

The MR scans were performed on a 1.5 T whole body scanner (Magnetom Sonata, Siemens Medical, Germany). In the imaging session, one T1w whole brain data set was acquired (MPRAGE, TR/TE/TI/α = 1.9s/3.9ms/1.1s/15°) with an isotropic resolution of 1 mm^3. A FLAIR data set was measured to identify individual lesion load (TR/TE/TI/Turbo Factor = 9s/108ms/2.4s/25; Δx = 1x1x4mm^3). In the fMRI scans, a T2*w EPI sequence was used (TR/TE/α = 2s/55ms/90°) with an in-plane resolution of 4x4 mm^2. Per volume, 20 slices (4 mm thick, 2 mm gap) parallel to the inferior borders of the corpus callosum were scanned in interleaved order. The fMRI runs were measured in a block design. Each block had 18 volumes; five baseline blocks altered with four task blocks. Anatomical data sets and all three fMRI runs were scanned in one session.

The severity rating of white matter lesions was done by an experienced neuro-radiologist using ARWMC Rating Scale (ARWMC: age-related white matter changes) [1] ranging from 0 (no changes) to 3 (severe changes). Subjects rated in the classes zero and one were pooled as "controls" and subjects in class two and three as "patients".

The fMRI data sets were post-processed using AFNI [2]. The post-processing included slice timing and motion correction, spatial smoothing with a Gaussian filter (FWHM = 8 mm), intensity normalization and realignment to the high resolution anatomical volume. Statistical maps were created for each subject and for each task by performing a multiple linear regression analysis. The ideal function was a boxcar function convolved with the hemodynamic response function. The whole brain signal time course and motion parameters were treated as regressors of no interest. The percent change maps were then transformed to Talairach space using the transformation parameters of the anatomical data set. For the second level analysis, only subjects were included which had shown less than 2 mm motion in all three fMRI experiments. Thus, the statistical maps of 10 patients (3 female, 67±7 a) and of 10 controls (5 female 60 ± 10) underwent a three factor analysis of variance (ANOVA). Group (patient/control) and task were treated as fixed factors and the subjects as the random factor (AxBxC(A)-ANOVA). Following statistical maps were created: first, a main effect map for each task class pooled over all subjects; second, a contrast map patients versus controls for each task class; and third, contrast maps between the different tasks, separately for patients and controls. The resulting t-maps were thresholded at a corrected significance level of $p<0.01$.

Results

Task specific activation was found in bilateral posterior parietal areas and in dorsolateral prefrontal cortices as well as in medial frontal areas. These regions showed a significant increase with task difficulty (see Fig. 1). No significant difference in the main effect was found for the contrast between patients and controls for all three tasks. However, in controls the contrast between the different tasks showed a significant and widely distributed increase of activation in both 2-back versus 0-back and 2-back versus alertness (Fig. 2, 3). In contrast, in patients only sparse increase of signal was found in medial frontal parts for 2-back versus 0-back (Fig.3) and no significant increase was detected in 2-back versus alertness.

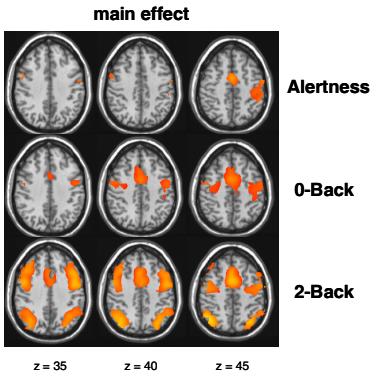

Fig.1: Main effect for all three tasks pooled over all subjects (t-scores, $p_{cor}<0.01$).

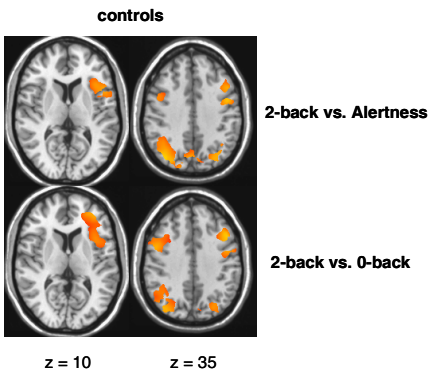

Fig. 2: Signal increase in controls for the 2-back task ($p_{cor}<0.01$).

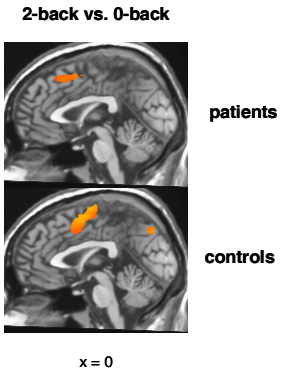

Fig.3: Sparse signal increase in patients compared to controls ($p_{cor}<0.01$).

Discussion

In our study, SVE patients showed reduced increase in functional response parallel to increasing difficulty of the presented tasks. Thus, short term memory processing is evidently different between patients and controls. Similar results were found in a study with multiple sclerosis patients [3]. The reduced increment in brain activity may be interpreted as reduced functional reserve and may indicate sub-clinical compensatory mechanisms or alternatively reduced inhibitory control in SVE patients.

References

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