

Changes in cerebral blood flow following successful psychotherapy combined with cortisol treatment in spider phobia

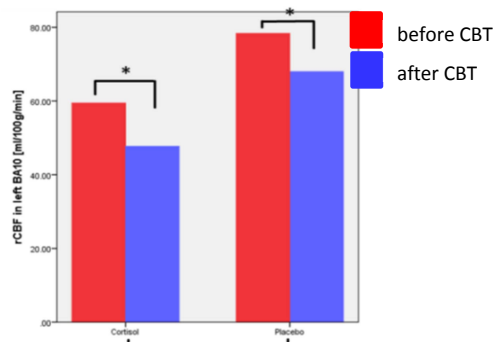
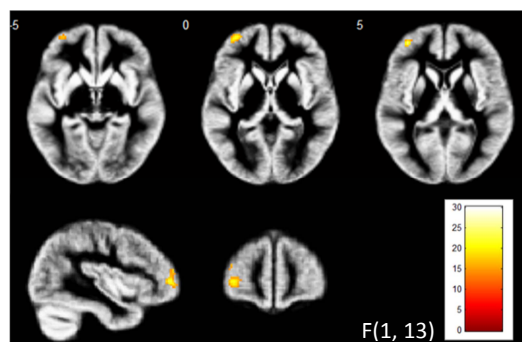
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Introduction: Neuroimaging approaches are increasingly applied to psychotherapy research, e.g. to identify changes in neuronal networks associated to emotion regulation after cognitive-behavioral therapy (CBT) of anxiety disorders. Recent studies show that cortisol ("stress-hormone") treatment reduces phobic fear in patients with anxiety disorders – possibly through reducing the retrieval of fear memory [1, 2]. Thus, the release of cortisol may represent an adaptive response to stress and phobic stimuli, respectively, by reducing fear symptoms. Stress-induced increase of cortisol has been shown to be associated with changes in regional cerebral blood flow (rCBF) as measured by arterial spin-labeling (ASL), which is a quantitative neuroimaging technique [3]. In this double-blind placebo-controlled study we investigated the therapeutic efficacy of exposure-based CBT in combination with cortisol administration and the associated changes in CBF.

Methods: ASL was measured in 15 patients with spider phobia before and 4 weeks after cessation of exposure-based group CBT. Therapy led to a significant decrease in phobic symptoms ($p < .001$). Before both ASL measurements the patients were exposed to color photographs of spiders. 1 hour prior to the picture task, patients either received a single dose of 20 mg hydrocortisone (cortisol group, $N=7$) or placebo (placebo group, $N=8$). CBT consisted of 2x2.5-hour exposure-based group CBT one week apart integrating exposures to living spiders. 1 h before each CBT session, patients received the same medication as before ASL. Imaging was performed in a 3T Siemens Magnetom Trio TIM system equipped with a 12-channel head coil. The pseudo continuous ASL parameters were: 13 slices, 6.5mm slice thickness, $FOV=230 \times 230 \text{ mm}^2$, $matrix=128 \times 128$, $TR/TE/t/PLD=3500/18/1720/1100 \text{ ms}$ and $FA=25^\circ$. A balanced labeling technique [4,5] was used with a mean slice-selective gradient (Gz) of 0.6 mT/m. 50 label/control-pairs were acquired. In addition, a 3D T1-weighted structural scan was run (modified driven equilibrium Fourier transform (mdeft) sequences: 176 sagittal slices with 1.0mm thickness, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, $TR/TE = 7.92/2.48 \text{ ms}$, $FA = 16^\circ$, $FOV = 256 \times 256 \text{ mm}^2$, matrix size = $256 \times 256 \text{ mm}$, and $Ti = 910 \text{ ms}$ for an optimal contrast-to-noise ratio) [6]. Matlab/SPM8 was used for preprocessing of imaging data and calculation of absolute CBF maps. ASL images were motion corrected and CBF was quantified using a single-compartment model (T_1 , 1650ms, labeling efficiency 0.85, blood-tissue partition coefficient 0.9). CBF images were coregistered to the T1 images, normalized into standard MNI space and smoothed with an 8mm FWHM Gaussian kernel. Voxel-wise analysis of variance (ANOVA) was calculated with group as the between-subject factor, and therapy as the within-subject factor.

Results: The most significant ROI resulting from the group x therapy interaction of the voxel-wise ANOVA was identified in the prefrontal cortex as the left BA10. Quantification and analysis of rCBF yielded significant main effects of group ($F(1, 13)=24.6$, $p < .0001$) and therapy ($F(1,13)=22.5$, $p < .0001$) associated with decreased CBF as an effect of therapy and treatment with cortisol.



Discussion: Insights into the neuronal mechanisms underlying effective treatment of spider phobia may provide important information for specified treatment of anxiety disorders. We could show that successful CBT is associated with a significant decrease in rCBF in the prefrontal cortex, which is consistent with existing literature [7]. This effect is potentiated in patients treated with cortisol; however rCBF is significantly decreased already before CBT in this region after cortisol intake. Hydrocortisone treatment might facilitate the effects of CBT integrating exposure therapy by reducing fear symptoms at confrontation with the phobic stimulus.

[1] Soravia L et al. (2006) PNAS [2] de Quervain DJF et al. (2011) PNAS [3] Wang JJ et al. (2005) PNAS, [4] Wu WC et al. (2007) Magn Reson Med [5] Dai W et al. (2008) Magn Reson Med [6] Deichmann R et al. (2004) Neuroimage [7] Johanson A et al. (2006) Appl Neuropsychol.