Acute effects of corticosterone on BOLD signal: a pharmacological fMRI study in rats at 7 Tesla.

M. I. Schubert¹, S. Droste², R. Kalisch¹, F. Holsboer³, J. M. Reul², D. P. Auer¹
¹Max Planck Institute of Psychiatry, Magnetic Resonance Study Group, Munich, Germany, ²Max Planck Institute of Psychiatry, Section of Neuropsychopharmacology, Munich, Germany, ³Max Planck Institute of Psychiatry, Munich, Germany

Synopsis
Thirteen adrenalectomized rats were examined by phMRI at 7 Tesla in order to map local changes in BOLD signal after an acute stress challenge with corticosterone (CORT, n=7) compared to vehicle injection (CON, n=6). Regional time courses of CORT versus CON showed a relative increase (1.0-1.2%) in BOLD signal in medial prefrontal cortex/anterior cingulate (mPFC/ACC). Averaged time courses of volume of interests identified post hoc in SPM map confirmed a positive response difference of CORT/CON in orbitofrontal cortex, caudate-putamen and mPFC/ACC. Acute rises of CORT appear to regionally increase BOLD signal being in line with stress-related activation of prefrontal circuits.

Introduction
Glucocorticoid (GC) hormones have been implicated in stress-related psychiatric diseases such as major depression, particularly in the presence of dysfunction of negative feedback signals of elevated GCs on the level of the mineralocorticoid and glucocorticoid receptors (GR) in the brain. Surprisingly little is known, however, about the acute cerebral effects of GCs. Therefore, the aim of our study was to evaluate local changes in blood oxygen level dependent (BOLD) signal after an acute challenge with corticosterone (CORT). To control for experimental stress induced activation of GRs, rats were adrenalectomized (ADX) and substituted with CORT (15 µg/ml) and sodium chloride (0.9%) in the drinking water.

Materials and Methods
Thirteen age-matched male Wistar rats were examined one week after ADX with BOLD-phMRI at 7 Tesla using a dedicated surface coil.

Animal Preparation and Experimental Procedure
Rats were anesthetized with 1.1% isoflurane and mechanically ventilated. For measuring the blood pressure and for taking blood samples an arterial catheter was put in the tail artery. For the administration of CORT (10 mg/kg bw) and vehicle a catheter was placed in the left lower back subcutaneous tissue. Rats were fixed with ear bars, a bite bar and a safety gate over the head. During the whole scanning time rats were monitored continuously. Blood samples were taken before and immediately after the phMRI (60 minutes after administration of CORT or vehicle) for determination of corticosterone and adrenocorticotropic hormone. After being removed from the MR scanner rats were decapitated under deep anesthesia.

MRI Protocol
For anatomical orientation RARE images (TR=5000 ms, TE=6.9 ms, Rare factor 16, spatial resolution 0.25 x 0.25 x 1 mm³) in three orientations were acquired. For phMRI, a RARE sequence (TR=1875 ms, TEeff=19.5 ms, 2 img/min, 70 min scan duration, matrix 0.36x0.36x1 mm³, 13 slices) was used. After a 10 min baseline, 10 mg/kg CORT dissolved in polyethylenglycol 300 (n=7) or the vehicle (polyethylenglycol 300, CON, n=6) was given subcutaneously.

Image Analysis
Regional time courses of the BOLD signal were analyzed with FUNtool Software (Bruker) in the following regions of interest: medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), left motor cortex, left hippocampus, thalamus/medial thalamus. For SPM analysis the brains of 11 animals (n=7 CORT, n=4 CON) were normalized on an internal template. The BOLD response from 30 to 60 minutes relative to baseline was compared between CORT and CON condition using a box car model. Contrasts were calculated within a fixed effects model. Averaged time courses were taken from volume of interests (VOI) identified post hoc in the SPM map as showing a strong or no response difference between CORT and CON.

Results
We observed a decrease of the mean BOLD signal of –0.8% in mPFC and ACC after vehicle injection as opposed to an increase of 0.2–0.4% after CORT starting at approximately 15 min after the injection. Thus, direct comparison of the two time courses revealed that CORT produced an absolute increase of 1.0–1.2% in the BOLD signal in mPFC and ACC. There were no changes in BOLD signal in the left motor cortex, left hippocampus and thalamus/medial thalamus. SPM comparison of CORT vs. CON between 30 to 60 minutes scan time (i.e. 20-50 min after CORT stimulus vs. vehicle) showed positive parenchymal BOLD-responses of CORT vs. CON in the orbitofrontal cortex (OFC), mPFC/ACC and in the caudate/putamen (CPu). Averaged time courses of VOIs identified post hoc in the SPM map confirmed a positive response difference in direct comparison of CORT vs. CON in the OFC, CPu and mPFC/ACC.

Discussion and Conclusion
These data suggest that acute rises of CORT (as occurring during stress) increase the BOLD signal in the mPFC/ACC, CPu and OFC. In physiological terms, it appears that glucocorticoid receptor activation eventually induces increased local blood flow due to neuronal activation. Interestingly, a recent human [¹⁵O]H₂O PET study revealed mixed patterns of both increased and decreased cortical and subcortical blood flow upon hydrocortisone. An alternative interpretation of our observations, however, may be a direct focal metabolic CORT-effect on glucose flux and oxygen extraction without altered neuronal activation.

References