Introduction: The post-stimulus undershoot is a well recognised component of the BOLD response [1]. However, the BOLD response originates from a complex interaction between cerebral blood flow (CBF), cerebral blood volume (CBV) and the metabolic rate of oxygen consumption (CMRO2), making the physiological origin of the post-stimulus undershoot unclear. Proposed mechanisms for the undershoot include: (i) elevated CBV once CMRO2 has returned to baseline whilst CMRO2 remains elevated or (ii) a reduction in CMRO2 below baseline, accompanied by a greater reduction in CBF [2]. In monkeys, the BOLD undershoot has been shown to be accompanied by a decrease in neural activity (LFPs and MUA) [3], suggesting mechanism (iii). Here, we use simultaneous EEG-BOLD-ASL during median nerve stimulation (MNS) to investigate the correlation between the undershoot and neuronal activity in humans for the first time. A consistent EEG feature on cessation of MNS is a rebound of the mu (8-13Hz) and beta (15-30Hz) frequency bands above pre-stimulus levels. This post-stimulus event-related synchronisation (ERS) of mu [4] typically lasts a few seconds; we suggest that the ERS reflects changes in neuronal activity which modulates the BOLD post-stimulus undershoot. Whilst close spatial agreement between beta PERS and the positive BOLD response has been reported in motor cortex [5], the temporal relationship between PERS power and the amplitude of the BOLD undershoot is unknown.

Hypothesis: We postulate a correlation between the magnitude of the PERS and the BOLD post-stimulus undershoot, which would provide new evidence of a neural component to the BOLD undershoot.

Methods: MNI and EEG data were acquired simultaneously using a Philips Achieva 3T MR scanner and a 64-channel EEG-precursor (ActiCap, Brain Products). 64-EEG channels and 14 BOLD-sequences of axial slices encompassing the primary somatosensory cortex (SI). A FAIR Double Acquisition Sensitive Blood Oxygenation Suppression (DABS) [6] sequence was used for simultaneous acquisition of background suppressed ASL and BOLD data (TR=2.6s; TE=13/33ms [ASL/BOLD], delay label=1400ms, 3x3x5mm³ voxels, 2121mm FOV, SENSE factor 2; background suppression at T1/T2=340ms/560ms). Data were acquired on 18 right-handed subjects (age=27±3yrs). MNS was applied to the right wrist (2Hz, 0.5ms duration pulses, Digitimer DS7A) at each individual’s motor threshold for thumb distension. Data were recorded over 40 blocks (10s/20s MNS/rest). Analyses were performed on a custom in-house written software and on SPM. Data were corrected for head motion and artefacts and performed on a high-pass filter (0.05Hz) on the BOLD data before analysis. HR data were time locked to MNS, and a specific frequency window of 0.5-1Hz was used to localise the mu response to MNS, based on digitised electrode positions and a spherical head model [9]. Virtual electrode timecourses of electrical activity were extracted from the peak pseudo T-stat location in contralateral sensory-motor cortex (S1/M1) cortex (active/passive window: 0-9.5s/20-29.5s). For each block, the mean stimulus response (0-5.5s), PERS (10.5-20s), and control window (25-29.5s) mu power values were calculated. For each subject, HR amplitudes and a significant difference in the lag of the falling edge of the BOLD/CBF response or control window mu power was observed. BOLD and ASL datasets were normalised to MNI template and spatially smoothed (5mm). A GLM analysis was performed in SPM using a boxcar regressor of the stimulation period convolved with the canonical HRF. A second level, group fixed-effects analysis was performed. Areas of significant negative/positive correlation of BOLD (p<0.05, FWE corrected) and CBF (p<0.001, uncorrected) data with the boxcar model were identified in contralateral ipsilateral sensorimotor cortex (SI/M1). The group-level conjunction of the significant BOLD and CBF regions was performed using individual’s SOIs (3x3x3 mm³) was weighted on the positive voxel overlap across subjects, both the positive (contralateral) and negative (ipsilateral) regions. BOLD and CBF single-trial haemodynamic responses (HRs) were extracted for each block from the BOLD ROIs; allowing direct comparison between CBF and BOLD responses. HRs were sorted into quartiles according to either the PERS stimulus on control window mu power. HRs were then converted to percentage change relative to the final 6s of the individual’s mean block HRF, and averaged over subjects.

Results: EEG: Figure 1 shows the significant difference in PERS mu power between the three quartiles and the variability across subjects. No significant correlation between PERS mu power and either stimulus response or control window mu power was observed. IMRI: The main BOLD/CBF signal response (at ~10 s) to MNS was positive in contralateral (Fig 2 purple) and negative in ipsilateral (Fig 2 green) SI/M1. In both the positive and negative BOLD/CBF regions the post-stimulus undershoot shows a BOLD/CBF-negative factor. Significant differences were observed across all MNI quartiles. The main BOLD/CBF response (at ~10 s) to MNS was positive in contralateral (Fig 2 purple) and negative in ipsilateral (Fig 2 green) SI/M1. No significant differences were observed across all MNI quartiles. BOLD/CBF responses were found when sorting according to control window mu power. ROIs from CBF peak T-stats showed similar effects of sorting on the undershoot (data not shown).

Discussion: Here, we provide the first evidence that the BOLD post-stimulus undershoot (<20s) is linked to post-stimulus changes in electrical oscillatory activity (10-20s) in humans. MNS blocks with higher post-stimulus mu power exhibited more negative BOLD/CBF undershoots in both positive and negative BOLD regions. This correlation was not observed when sorting data according to stimulus or control mu power, providing further evidence that our findings truly reflect correlation of the post-stimulus neuronal and IMRI signals. The difference in the HR lag and peak amplitudes observed when HRs were sorted by PERS mu power is not believed to be caused by the neuronal activity occurring between 10-20s (time window of PERS mu), as the haemodynamic response delay must be considered. Instead we postulate that differences in PERS mu power are a consequence of differences in stimulus-driven (0-10s) neuronal activity across frequency bands other than mu and that this underlies the differences in the main peak BOLD/CBF responses and lag. Since mu ERS is commonly believed to reflect inhibitory neuronal activity [10], we hypothesise that a change in the balance of excitatory/inhibitory activity in sensory-motor cortex upon termination of stimulation causes a change in CMRO2. We show a concordant effect on BOLD and CBF signals post-stimulus which may be triggered by such changes in neuronal activity [3]. The observed BOLD undershoot would require changes in CBF to be greater than those of the CMRO2, as proposed in mechanism (ii) and similar to the mechanism of the main BOLD response.