Feasibility and repeatability of ASL-based phMRI after a single dose oral challenge as a tool for assessing 5-HT function

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Introduction Pharmacological MRI (phMRI) is a promising new imaging method in which neuronal function is modulated pharmacologically while simultaneously brain functional MRI is collected. For this study, focus was laid on challenging the serotonergic (5-HT) system by administration of a selective serotonin reuptake inhibitor (SSRI). So far, most 5-HT phMRI studies investigated the direct effects of a drug challenge using intravenous administration or the effects of chronic drug pre-treatment on neurotransmitter function[1]. It would however be less invasive to use a single oral dosage of the challenging drug. Few studies have tried this, using an indirect measure of neurotransmitter function in the form of a task-related fMRI design[2] and using blood-oxygenation-level-dependent (BOLD) contrast, which is not a quantitative measure and known to vary considerably over time. It is therefore considered unfeasible to give a drug orally and later on measure its direct effect on (resting-state) phMRI BOLD signal, especially considering the long T-max values oral drugs typically have[3]. This problem may be overcome by using CBF- or CBV-based techniques, such as arterial spin labeling (ASL), which measures perfusion directly and is more reproducible over time[4]. To our knowledge, only one study investigated the effects of an oral SSRI challenge using ASL-based phMRI[5]. However, in order to be a reliable index of neurotransmitter function, the used method should also have good repeatability. The purpose of this study was therefore to verify the feasibility and investigate the repeatability of ASL-based phMRI after a single dose oral challenge in assessing cerebral 5-HT function.

Methods Twelve healthy right-handed female volunteers (mean age 23 ±3 years) were included. Participants were scanned on 3 different days, with an interval of 2 weeks (15 ±2.5 days) to ensure washout of the challenge. Each MRI session consisted of 1) a baseline scan, followed by intake of the oral challenge (citalopram (16mg) or placebo) and 2) a second scan 2 hours (123 ±4 min) after intake. In two out of three MRI sessions an oral 5-HT challenge with citalopram was given. The placebo session took place (pseudo-randomly) on the first or the second day. All subjects were blinded to the type of challenge given. On a 3.0 Tesla Philips MR scanner, a pulsed ASL (PULSAR) sequence[6] was used to measure cerebral blood flow (CBF-)maps. Imaging parameters: TR/TE 3000/14ms; FOV 240×240mm2; matrix size 80×79; 17 slices; thickness 7mm, no gap; gradient echo single shot EPI; SENSE 2.5; post-labeling delay 1.2-2s; 50 dynamics; labeling gap between center of the imaging volume and labeling slab was 25mm. Also, high resolution 3DT1-weighted structural scans were acquired for each subject and non-rigidly normalized to a population-based average using DARTEL. The non-rigid transformations were applied to CBF-maps previously registered to grey matter masks and smoothed with FWHM=6mm. Average CBF-values were determined using predetermined regions-of-interest (ROIs) from the Harvard-Oxford structural atlas provided within FSL (figure 1). The following ROIs were included based upon previous literature[1,3]: gray matter (GM), superior frontal gyrus (SFG), inferior frontal gyrus, medial frontal gyrus, anterior cingulate gyrus, amygdala, thalamus, hippocampus and caudate. Effect of placebo or citalopram challenge compared to baseline was determined using a Wilcoxon signed-rank test. Repeatability of CBF values was interpreted using Bland-Altman plots, the coefficient of repeatability (CR) and the index of repeatability (IR)[7].

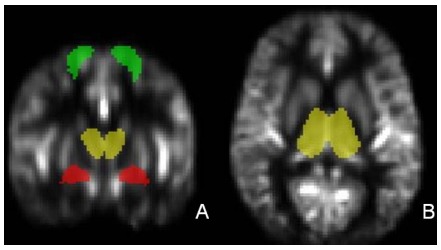

Fig. 1 Mean perfusion map averaged over all subjects after registration to standard space. A) Coronal section with SFG (green), thalamus (yellow) and amygdala (red) mask superimposed, B) axial section with thalamus mask superimposed.

Results In none of the analyzed regions an effect of the placebo challenge was found. The placebo session was therefore used to determine repeatability of mean CBF-values within one session (time interval between scans 123 ±4 min). The largest likely size of difference between two measurements on the same subject (=CR) for the GM was 11.83 ml/100g/min which is considered good repeatability (figure 2). Preliminary results show significant effects of citalopram challenge in the SFG (effect size session 2: +5.7 ml/100g/min, p=0.016), thalamus (effect size session 2: +5.9 ml/100g/min, p=0.010) and amygdala (effect size session 1: -8.6 ml/100g/min, p=0.005). Repeatability of mean CBF values within one session in these specific regions is also given in figure 2 and can be considered to be acceptable (amygdala) to good (SFG). However, none of the effects of citalopram could be reproduced. An example of the data from the two citalopram sessions in the SFG is given in Figure 3.

	GM	Amyg	Thal	SFG
CR	11.83	20.89	16.44	8.56
IR (%)	21.45	33.53	30.35	16.24

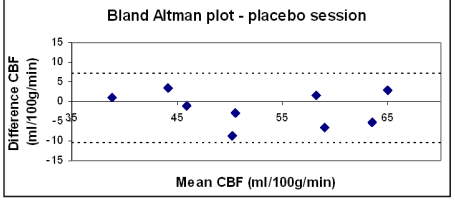

Fig. 2 CR and IR values for GM, amygdala, thalamus and SFG. Bland Altman plot of the placebo and baseline scan in the SFG, dotted lines indicate mean difference ± 1.96SD.

Discussion Although good within-session repeatability of the ASL signal was found for the investigated brain regions, the effects of the oral citalopram challenge could not be repeated within two sessions. We attribute these contradictory findings between the two citalopram sessions to the limited sample size of our study. Based on the CRs measured for the different regions, sample sizes in the order of 15-20 subjects are needed to detect SSRI-induced changes in CBF that exceed the expected variation in the ASL signal. Furthermore, there are probably also individual physiological differences in activity of the 5-HT system to consider. Concluding, our study illustrates the usefulness of ASL in phMRI, but at the same time our findings underline the necessity of large sample sizes. It may be that even with more reproducible sequences such as pCASL[5], variations in ASL signal and 5-HT function are still too high to use this method as a diagnostic tool for assessing cerebral 5-HT function in individual subjects.

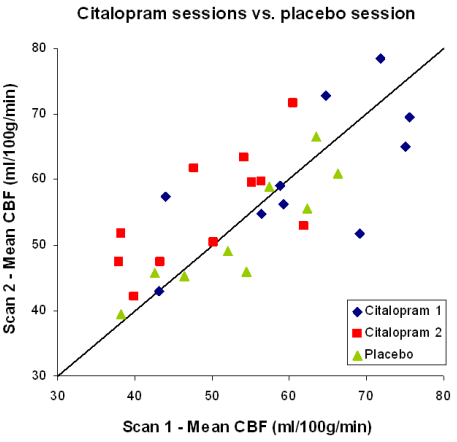

Fig. 3 Scatter plots of the mean CBF values of the baseline (scan1) and challenge scan (scan2) in the SFG. The black line indicates point of no difference. The first citalopram session (blue) shows no effect compared to its baseline scan (Wilcoxon signed-rank test; Z=-0.357, p=0.721). A similar result is seen in the placebo session (green; Z=-0.866, p=0.368), while the second citalopram session (red) shows a significant increase of CBF after citalopram intake (Z=2.041, p=0.016).

References [1] McKie et al., Psychopharmacol (2005) 180:680; [2]Völlm et al., Eur J Neurosci (2006) 23:552; [3]Anderson et al., Neuropharmacol (2008) 55(6):1029; [4]Gevers et al., Am J Neuroradiol (2009) 30(5):968; [5]Chen et al., Proc ISMRM 18 (2010);720; [6]Golay et al., MRM (2005) 53:15; [7]Bland and Altman, Lancet (1986) 307.