Methylphenidate causes changes in the amplitude and latency of the breath-hold response function

T. Van der Doef1,2, F. O. Zelaya3, S. Lee2, A. Pauls1,4, and M. Mehta2

1VU University Medical Centre, VU University, Amsterdam, Netherlands, 2Centre for Neuroimaging Sciences, Institute of Psychiatry, London, United Kingdom, 3Centre for Neuroimaging Sciences, Institute of Psychiatry, London, London, United Kingdom, 4VU University, Netherlands

Introduction
One of the most useful applications of BOLD calibration techniques is their potential ability to reduce the inter-subject variance in BOLD-based studies of the effects of psychoactive drugs on cognition. Many of these drugs produce non-neuronal (e.g. vascular) effects at certain doses, which can limit the sensitivity of comparisons across groups. In this study we used a modified version of a breath-hold (BH) paradigm (1) to explore the regional differences in the BH response elicited by the administration of a catecholamine re-uptake inhibitor (methylphenidate), used in the treatment of attention deficit hyperactivity disorder.

Method
Sixteen healthy male volunteers (mean age 22.7 ± 2.6) were scanned on two occasions (at 1-week intervals) and received randomised administration of methylphenidate 40mg or placebo 75 minutes prior to scanning. The BH paradigm consisted of 5 blocks paced breathing (36s, 3s inspiration, 3s expiration), alternated with breath hold periods (16s, after expiration); ending with a normal breathing period of 40s (total=5min). Scans were performed in a 3-T GE Signa HDX scanner using a GR-EPI protocol, TR/TE = 2000/25, thirty-nine 3.3mm near-axial slices, ASSET factor = 2.0. A pneumatic belt was used to monitor compliance with the paradigm. Heart rate was recorded throughout the scan. Image data were pre-processed using SPM5 and signal time courses (Fig. 1) were extracted from regions of different dopamine transporter availability (from high to low: putamen, caudate nucleus, thalamus, fronto superior medial cortex (FSMC) and cerebellum) with MARSBAR (Brett et al. 2002). Numerical data were analysed with SPSS.

Results
Scans were corrected for subject motion and the six motion parameters were included as regressors in the model. The averaged grey matter signal from the placebo and methylphenidate sessions showed a periodic signal variation in which the peak of the BH response occurred approximately 24s after the start of the 16s breath-hold period. The Finite Impulse Response Function Model (2) with a time window of 52s and resolution of 2s, was initially used to formally confirm that the canonical HRF was insufficient to describe the signal elicited in the paradigm. Signal time courses were then extracted from the pre-determined regions of interest. After linear detrending, mean-centred signals were averaged across all blocks (Fig. 1), significant amplitude reduction after methylphenidate was found only in the FSMC (P<0.03). Methylphenidate caused significant reduced latency to half-maximum amplitude (P<0.02) in the putamen, caudate nucleus and the FSMC.

Discussion
Methylphenidate is known to act as a vaso-constrictor via increases in extra-cellular noradrenaline and dopamine. Here we show that methylphenidate administration decreases the latency of the BH response across several brain regions. These changes in latency are not correlated with the dopamine transporter density and may be related to a decrease in rCBV (2). The increase in the BH response amplitude in the FSMC may arise from a reduction in baseline rCBF caused by vasoconstriction (3). Further work is being carried out to assess these changes on the basis of the regional differences in noradrenaline transporter availability. These data also demonstrate that differences found in BOLD-based studies of the modulation of cognition after administration of methylphenidate, may be confounded by the non-neuronal effects induced by this compound.