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

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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.

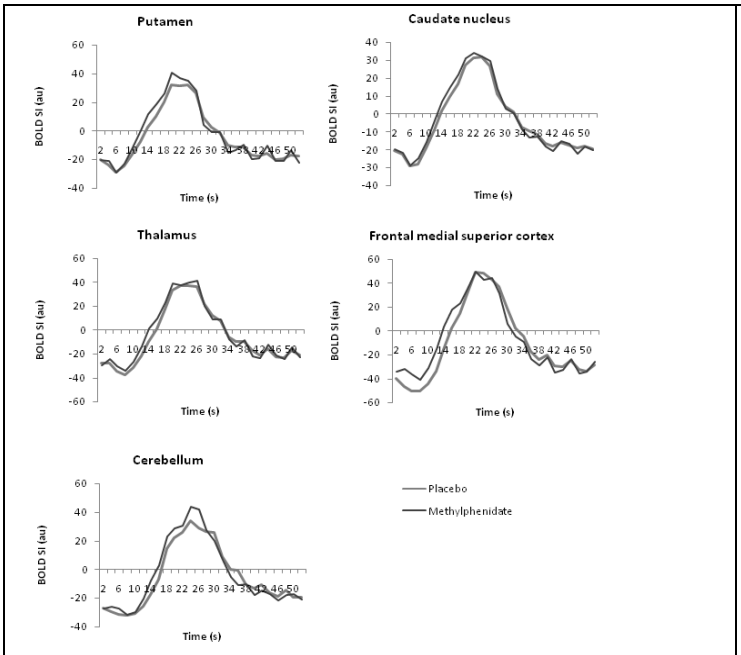

Figure 1: BOLD signal changes from the BH paradigm after methylphenidate 40mg and placebo, averaged across the 3 central blocks of the paradigm, in 5 pre-selected ROIs (putamen, caudate nucleus, thalamus, fronto-medial cortex and cerebellum).

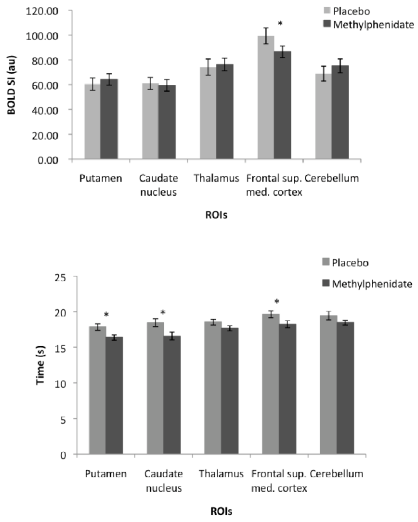

Figure 2: Differences in signal amplitude and latency in the BH response function of the five chosen ROIs. An asterisk marks those that are statistically significant for this dose of Methylphenidate (n=16).

REFERENCES

1- Scouten et al, Neuroimage 43, 250-257 (2008) **3**- Mulderink et al, Neuroimage 15, 37-44 (2002) **2**- Glover et al, Neuroimage 9, 416-429 (1999)
4- Brett M, Anton J-L, Valabregue R, Poline JB (2002) Region of interest analysis using an SPM toolbox. In *NeuroImage* p Abstract 497**.**