Comparable spatio-temporal characteristics but differences in metabolism-CBF coupling in intrinsic connectivity networks identified from simultaneous BOLD and CBF

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Introduction: Spontaneous, low frequency fluctuations in fMRI signals are highly correlated between functionally connected brain areas [1]. Intrinsic connectivity networks (ICNs) can be reliably identified from these coherent fMRI signals during both rest [1] and stimulation paradigms [2]. This provides a valuable methodology for studying the functional architecture of the human brain in both health and disease. Studies of ICNs have been almost exclusively conducted using BOLD contrast, although similar, coherent fluctuations in cerebral blood flow (CBF) have been reported in the default mode network (DMN) [3,4] and motor cortex [5], with good spatial agreement with BOLD data. CBF signals are suggested to be more closely related to neuronal activity than BOLD, thus a detailed spatio-temporal comparison of ICNs using concurrent BOLD/CBF measurements is important. We use independent components analysis (ICA) of simultaneous BOLD and CBF data to interrogate the DMN and dorsal attention network (DAN) during median nerve stimulation (MNS). The concurrent BOLD/CBF measures enable us to investigate the coupling between stimulus-driven changes in cerebral metabolic rate of oxygen ($CMRO_2$) and CBF in both the DMN and DAN.

Methods: MNS was applied to the right wrist (2Hz, 0.5ms duration pulses, Digitimer DS7A) of eighteen, right-handed subjects (age=27±3yrs) at an amplitude just above each individuals' motor threshold for thumb distension. Data were recorded over 40 blocks (10s/20s MNS/rest). A FAIR Double Acquisition Background Suppression (DABS) sequence [6] was used for concurrent acquisition of ASL and BOLD data (Philips Achieva 3T scanner, background suppression at TI1/TI2=340/560ms; label delay=1400ms; TR=2.6s, TE_{ASL}/TE_{BOLD} =13/33ms, 3x3x5mm^3 voxels, 212mm FOV, SENSE factor 2, 10 contiguous axial slices). Cardiac pulse and respiration were recorded using the scanner's physiological logging.

Analysis: RETROICOR was used to reduce physiological noise in the BOLD data. FLIRT (FSL) was used for motion correction. Three subjects were excluded from further analysis due to gross head movement (>3mm). ASL data were interpolated to an effective TR of 2.6s, and tag-control pairs then subtracted to create perfusion-weighted images. BOLD and CBF data were smoothed with a 5mm kernel and registered to the MNI standard brain. GLM analyses were 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 for both positive and negative contrasts. *Spatio-temporal correlations:* Separately for BOLD and CBF, data were temporally concatenated across all subjects and MELODIC [7] used to decompose the group data into 25 independent spatial maps and their associated time-courses. Independent component (IC) spatial maps of the DMN and DAN were identified. Dual-regression [8] was then used to identify individual subject timecourses and spatial maps for each ICN. The following analyses were then performed for both the DMN and DAN. Maps were thresholded at $p<0.05$, Z-statistic=3 (group) and Z=6 (individual) and the conjunction between BOLD and CBF regions calculated. The correlation between BOLD and CBF time-series for each subject was calculated and averaged across the group as a measure of the temporal similarity between the BOLD and CBF signals. Single-block (0-30s) BOLD and CBF responses were extracted, and converted to percentage signal change relative to the last 6s of the block. BOLD and CBF responses were averaged across blocks and subjects. *$CMRO_2$ estimation:* For each subject, the maximal signal change occurring in the first 20s (i.e. the period of MNS-induced signal change) of the mean BOLD response was identified. The equivalent mean CBF change at that time was then found. From these data, the Davis model (Eq. 1) [9] was used to estimate $CMRO_2$ for each subject, and the group $\Delta CMRO_2/\Delta CBF$ coupling ratio, $\boldsymbol{n}$. $\boldsymbol{M}$ values for DMN and DAN were not determined here and are unknown from literature. However, literature suggests the variability within grey matter is small compared to that between subjects; with a lower bound of $\boldsymbol{M}$ at 3T of ~6% [10]. Therefore $\boldsymbol{M}$ values of 6.4 [11], 10.6 (mean) and 14.9% [12] (scaled to a field strength of 3T and TE=33ms) were used, taking Grubbs constant, $\boldsymbol{\alpha}$=0.2 [13], and $\boldsymbol{\beta}$=1.2.

Results: *Spatio-temporal correlations:* DAN and DMN were not identified from conventional GLM analysis, probably due to the passive nature of the task and the variability in ICN modulation across blocks. Therefore, ICA was used to detect coherent changes occurring concurrently in BOLD and CBF data during MNS. The group BOLD and CBF response to MNS was negative in the DMN (Fig 1A), and positive in the DAN (Fig 1B). A high degree of spatial overlap was observed between BOLD and CBF ICNs for both DMN (Fig 1A) and DAN (Fig 1B) at the single subject level (DMN=61±14% [= overlap/total active BOLD&CBF voxels] expressed in percent, DAN=53±10%) and group level: DMN=67%; DAN=46%. The temporal correlation of BOLD and CBF changes was significant ($p<0.05$) in 12 subjects for both DMN (R=0.28±0.19 group mean ± std) and DAN (R=0.21±0.12). *$CMRO_2$ estimation:* The group correlation of BOLD and CBF changes was negative in DMN (Fig 2A) and positive in DAN (Fig 2B) with data points crossing the $CMRO_2$ isocontours for both ICNs. Higher coupling ratios ($\boldsymbol{n}$) were found in the DMN than DAN (Fig 2C), regardless of the value of $\boldsymbol{M}$ (even if $\boldsymbol{M}$=100%).

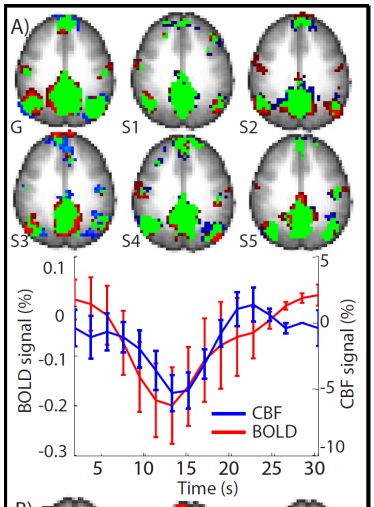

Fig 1. ICA identified DMN (A) and DAN (B) spatial maps for group (G) and representative subjects (S1-S5) CBF (blue), BOLD (red) and conjunction (green); with group mean timecourses of the response to MNS

$$\frac{CMRO_2}{(CMRO_2)_0} = \left(1 - \frac{\frac{\Delta BOLD}{BOLD_0}}{M}\right)^{1/\beta} \left(\frac{CBF}{CBF_0}\right)^{1-\alpha/\beta} \quad (1)$$

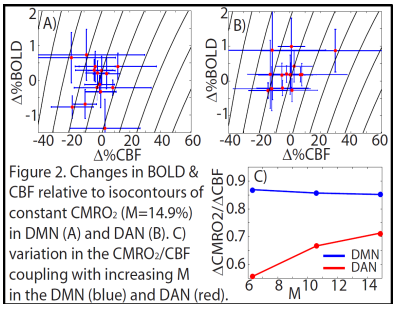

Figure 2. Changes in BOLD & CBF relative to isocontours of constant $CMRO_2$ (M=14.9%) in DMN (A) and DAN (B). C) variation in the $CMRO_2$/CBF coupling with increasing M in the DMN (blue) and DAN (red).

Discussion: The spatio-temporal patterns of signal fluctuations in the DMN and DAN are highly comparable in BOLD and CBF data. Our investigation of $CMRO_2$ suggests a different metabolism/CBF coupling in these two ICNs. In both ICNs, calculated values of $\boldsymbol{n}$ are higher than previously reported. However, this is partially due to our use of $\boldsymbol{\alpha}$=0.2, as suggested by recent experimental work [13]. Using the original value of $\boldsymbol{\alpha}$=0.38, and $\boldsymbol{M}$=10.6% gave $\boldsymbol{n}$=0.52/0.71 for the DAN/DMN, similar/larger than previously found in sensory cortex [11]. A difference in $\boldsymbol{n}$ between deep and cortical grey matter has previously been reported [11] despite $\boldsymbol{M}$ values being similar in both regions. Therefore, our higher $\boldsymbol{n}$ for the DMN could be explained by a larger proportion of this ICN comprising deep grey matter (i.e. precuneus) compared with the DAN. Coupling differences between ICNs suggest a reduced responsiveness of CBF in the DMN compared with the DAN, which may be due to differences in vascular biomechanics or control by the sympathetic nervous system [11]. Alternatively, an altered BOLD mechanism may underlie $CMRO_2$ variations in the DMN. Our findings are in contrast to a recent study that reported similar $\boldsymbol{n}$ values in task-negative DMN to those found in task-positive regions [4]. However, this discrepancy could arise from the use of BOLD measures from an ASL sequence with TE=17ms in [4], compared to our use of a DABS sequence optimised for BOLD and CBF; or from the use of a cognitively engaging task to induce strong DMN deactivations [4], compared to our passive MNS task. Our work demonstrates the importance of simultaneous BOLD/CBF measures for relating coherent BOLD signal fluctuations in ICNs to physiological variables, such as the $CMRO_2$/CBF coupling. Further investigation of the source of the observed differences between DMN and DAN is important to improve understanding of the healthy brain's functional architecture and the significance of changes that occur in disease conditions.

References [**1**] Damoiseaux et al PNAS **103**(37):2006. [**2**] Sadaghiani et al. J.Neurosci **30**(30):2010. [**3**] Zuo et al Neuroimage **48**(3):2009. [**4**] Lin et al Cerebral cortex **21**(4) 2011. [**5**] Chuang et al Neuroimage **40**(4):2008. [**6**] Wesolowski et al ISMRM, **6132**:2009. [**7**] Beckmann & Smith IEEE Trans. Med. Imag. **23**:(2004). [**8**] Beckmann et al HBM, San Francisco. 2009. [**9**] Davis et al PNAS 95:1998. [**10**] Gauthier et al Neuroimage 54(2) 2011. [**11**] Ances et al Neuroimage 39(4) 2008. [**12**] Kastrup et al Neuroimage 15(1) 2002. [**13**] Chen et al Neuroimage **53**(2):2010.