VEssel-ReactivitY-CorrecTed fmri Reveals NOvel PATterns of AGe-Related cHANGES in BraIn ACTIVITY

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INTRODUCTION: Cognitive aging studies using BOLD fMRI have revealed a wealth of information about the aging brain. The findings are typically represented by an age-related signal decrease in posterior regions such as visual areas and medial temporal lobe, which is interpreted as an age-related degradation in neural circuitry (1). These findings are nicely complemented by observations of an increase in frontal activations especially in right dorsolateral prefrontal cortex (DLPFC), which is interpreted as compensatory activations using neural reserve (2,3). Despite this seemingly coherent model, an intuitive yet largely unaddressed issue is that brain vascular health also declines with age (4) and, since BOLD is a vascular-based signal, the above fMRI findings could be entirely or at least partly explained by an age-related change in vascular property (5,6). Few previous studies have considered this issue and no lifespan studies (not just two extreme age groups) have taken this factor into study design. Here, we conducted an fMRI study in 132 healthy subjects aged 20-89 years old using an episodic memory (EM) task. In the same session, cerebrovascular Reactivity (CVR) was measured via inhalation of CO2 gas mixture, allowing a quantitative mapping of vasodilatation capacity in the same voxels that fMRI signals were measured from. Reactivity-corrected fMRI signal revealed that no brain regions manifested age-related decline in neural activity (under similar task performance), not even in the occipital cortex. Instead, age-related fMRI signal increase was observed throughout the brain with the effect in frontal regions being most prominent. These findings shed novel insights on age-related changes in neural activity and provide an exemplary illustration that vascular decline should be considered in ALL aging studies using fMRI as a tool.

METHODS: A total of 132 subjects from 20-89 years old were recruited using criteria typical for cognitive aging studies. They have a minimal MMSE score of 26, at least a high school education, and corrected vision of 20/10. Their age and gender distributions are shown in Table 1. All MRI measurements were performed on a Philips 3T MRI scanner. For the EM fMRI task, each subject received 3 fMRI runs with 32 pictures in each run. Each picture appeared for 3s followed by a fixation period of 4-17s (randomized). The subjects were instructed to determine if there is water in the picture and to press buttons in their right hand accordingly. All subjects performed this task accurately. Tasks of similar type are widely used in previous aging studies (1). Standard BOLD fMRI imaging parameters were used: TR/TE=2000/25ms, voxel size 3.4x3.4x3.5mm³, duration 5.75 min per run. CO2 is a potent vasodilator and, like acetazolamide (Diamox), it can be used to evaluate vascular elasticity and reserve. For the CO2 inhalation task, the subject breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while BOLD EPI images were acquired continuously. This short-duration breathing paradigm has been shown to improve subject comfort yet maintaining data quality (4,7). End-tidal CO2, the CO2 concentration in the lung and thus arterial blood, is recorded throughout the breathing task and a regression analysis between this signal and the MRI time course yields the Cerebrovascular Reactivity (CVR) map in the unit of %BOLD/mmHg. The CVR and fMRI data were then analyzed in similar task conditions. CVR signal was calculated as the contrast between picture viewing and fixation. FMRi signal correction was based on a previous report and was simply scaling the signal using CVR, i.e. fMRI=fMRI/CVR (8,9).

RESULTS and DISCUSSION: Fig. 1 shows fMRI activation maps. Robust activation is seen in early visual areas, medial temporal lobe (MTL), right inferior frontal gyrus (IFG) and left IFG. These four regions were therefore used in the ROI analysis. Fig. 2a (blue) shows age-related differences in the uncorrected fMRI signals. Consistent with other previous reports, visual area (p=0.05) and MTL (p=0.02) showed age-related decrease (1). Previous reports also suggested that age-related over-recruitment or compensatory responses are more pronounced in the right frontal region (p=0.002) than that on the left side (2,3). This pattern was also observed in our results (Fig. 2a). These data, however, have not accounted for vascular changes in aging. Decade-by-decade CVR maps are shown in Fig. 3 and ROI values are shown in Fig. 2b. As can be seen, an age-related reactivity decline is evident in all regions examined. Therefore, the loss of vascular reactivity itself could result in fMRI signal decrease independent of any true neural differences. For regions manifesting age-related fMRI decrease such as visual areas and MTL, the observations could be partly or entirely due to vascular effect rather than neuronal effect. A false negative error could also occur when age-related neural over-recruitment is offset by the reactivity decline, resulting in no apparent changes in the measured fMRI signal. Using adjustment method described in the Method section, one can correct the fMRI signal using CVR. The corrected fMRI signal is shown in Fig. 2a (red). It can be seen that age-related over-recruitment is now seen in both left and right frontal regions (both p<0.001). Importantly, none of the regions examined showed a signal increase with age. Voxel-wise analysis revealed patterns of similar nature (Fig. 4).

To our knowledge, the present report is the first cognitive aging study that interpreted fMRI findings in the context of vascular changes. Our observations provide strong evidence of a need to re-examine previous fMRI aging literature and suggest that previous studies may have over-estimated age-related decline while under-estimating the extent of compensatory over-recruitment. The reactivity-corrected fMRI data suggested no evidence of age-related decline in neural activity (under similar task performance).


Table 1. Subject information

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Fig. 1 Activation map from group level one-sample t test (N=132). Uncorrected p<0.001, k>200.

Fig. 2 Scatter plots of the ROI analysis. (a) fMRI signal changes with age. Red color indicates uncorrected fMRI signal. Blue color indicates CVR corrected fMRI signal. (b) Regional CVR changes with age. Each dot represents the mean value of each decade. Error bars are standard deviation, p<0.05 is considered significant.

Fig. 3 Decade-by-decade CVR maps.

Fig. 4 Voxel-based analysis of age-related increase (warm color) and decrease (cold color). Uncorrected p<0.005, cluster size k>200.

INTRODUCTION: In diffusion neuroimaging, there are two possible problems due to subject motion: i) images acquired with different diffusion directions are misaligned, leading to erroneous calculation of diffusion parameters, and ii) the diffusion direction being acquired when motion occurs can have signal dropouts. Multiple strategies, both retrospective [1] and prospective [2-6] have been proposed for dealing with this problem. In this work we developed a novel prospective motion correction method for multi-slice single shot diffusion weighted EPI. The technique is similar to the volumetric EPI navigator approach that has been shown for morphometric brain imaging [7].

METHODS: Rigid body navigation is achieved using non diffusion encoded low resolution single shot EPI images as motion navigator (EPI Nav) during the diffusion scan. Two approaches are demonstrated. In the first approach (integrated navigation, Fig 1), a low resolution EPI readout is placed after the 90° excitation pulse and before the diffusion encoding gradient. A corresponding fill time is inserted after the 180° pulse to maintain TE symmetry for the spin echo condition. In this study a 7.5 ms readout was used for EPI Nav leading to a 15 ms increase in TE per slice. In the second approach (interleaved navigation, Fig 2), the EPI Nav and diffusion acquisitions are decoupled. Since acquiring slice M for diffusion, slice N is acquired with a 10° flip for EPI Nav. In this work the diffusion series was acquired in 2 interleaves, so the slices M and N were set to be adjacent in space, but TR/2 separated in time in the diffusion scan. For typical TRs of 7-9 sec such a low flip excitation should result in negligible signal loss in the diffusion acquisition. For the interleaved method the EPI Nav acquisition took 10.5 ms per slice. For both techniques over the course of a TR a non diffusion encoded low resolution volume is created from the EPI Nav slices and used for prospective motion correction based on the 3DSPACE method which uses a 3D rigid body motion model [8]. The first such volume is used as the reference position by the 3DSPACE algorithm. The EPI Nav images are reconstructed using the real-time feedback framework on the scanner and an additional 50 ms delay is introduced at the end of each TR to enable real-time slice position updates for the next TR, based on motion correction. Five healthy volunteers were scanned with both motion correction techniques, and with a standard non motion corrected single shot EPI sequence. To evaluate the efficacy of motion correction, subjects were deliberately instructed to follow a predefined motion protocol during all three diffusion scans. Imaging was performed on a 3T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen). Parameters for the diffusion scan were: FOV: 220x220 mm², matrix: 128x128, b = 1000 s/mm², 60 slices with 2 mm thickness, TE 73 ms, TR 7600 ms, 30 diffusion directions, b/w = 1396 Hz/pixel, GRAPPA factor = 2. Parameters for the EPI Nav scan were: FOV: 256x256 mm², matrix: 32x32, partial Fourier factor = 0.66, b/w = 4596 Hz/pixel, 60 slices with 2 mm thickness (same as diffusion acquisition). For the integrated scheme, TE 88 ms, TR 8610 ms. For the interleaved scheme: TE 73 ms, TR 8300 ms. To demonstrate the independence of the proposed techniques from the b-value, an additional diffusion scan with b = 3000 s/mm² and 60 dirs was collected in one volunteer.

RESULTS: Fig 3 shows the detected rotation and translation parameters, sample EPI Nav images and a single direction diffusion weighted image (DWI) for both motion correction techniques, for two different b-values. Since the EPI Nav image is not diffusion encoded, it has good SNR even for a b-value of 3000 and gives reliable motion estimates. Fig 4 shows sample images from both motion correction techniques (top row, 4a: integrated, 4b: interleaved), compared with the non motion corrected sequence (bottom row in both 4a and 4b). The improvement in trace weighted (TW) and fractional anisotropy (FA) images in both motion corrected sequences is apparent. In addition, to evaluate the difference in signal level in the diffusion images between the corrected and uncorrected methods signal ratio in a white matter ROI was measured in the TW image. The integrated motion correction method had a 17.7% signal decrease (due to the increased TE); whereas the interleaved motion correction technique had a 0.57% signal decrease.

DISCUSSION AND CONCLUSION: We demonstrated a novel prospective motion correction technique for diffusion neuroimaging. The proposed methods work independent of the b-value used and do not need retrospective adjustment of the b-matrix. The compromise for the integrated method is the TE and TR increase and the corresponding signal decrease while the interleaved method requires only a small (~10%) increase in minimum TR.


ACKNOWLEDGEMENT: Andre van der Kouwe and M. Dylan Tisdall are supported by: NIH R21MH096559, R01HD071664, R21EB008547, R33DA026104, P41RR014075, and Ellison Medical Foundation.
The Electrophysiological Basis of Resting State Networks

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Introduction: In recent years, a great deal of fMRI literature has focused on investigating the structure and function of brain networks. Many such studies have employed ‘resting state’ fMRI recordings to delineate a set of networks, some associated with simple sensory processing (visual, auditory, motor etc.) and some associated with higher-level processes (e.g., the dorsal attention network, default mode network and salience network). These networks appear to be integral to human brain function; further, abnormal network connectivity is thought to be responsible for pathological conditions (e.g., schizophrenia). Gaining a complete understanding of such phenomena therefore represents a key goal for neuroimaging. BOLD fMRI delineates networks with unparalleled spatial resolution. However, it remains an indirect measure of ‘brain activity’ and neither the most rapid temporal dynamics nor the electrophysiological basis of network function can be assessed using fMRI alone. Magnetoencephalography (MEG) is a non-invasive technique that allows a more direct assessment of electrical brain function by assessing magnetic fields associated with synchronous current flow in pyramidal neurons in the cortex. Previous work5,6,7,8 has begun to highlight the ability of MEG to measure functional connectivity between network nodes, and such measures have also shown similarity with fMRI9,10. In this abstract we report the results of a resting state MEG study that independently identifies multiple brain networks in MEG data. We compare these electrophysiological networks directly to previously published work in fMRI11 and show significant similarity between modalities.

Methods: Ten healthy participants took part in the experiment. Subjects were asked to lie in the MEG scanner whilst 300s of resting state data were acquired using a 275 channel CTF MEG system (sample rate 600Hz) in 3rd order gradiometer configuration. Co-registration of MEG data to 3T anatomical MRI (MPRAGE, 1mm3) was achieved using head digitisation and surface matching. Data were filtered into frequency bands of interest and projected from sensor space to source space using a beamformer spatial filter. For each voxel in source space, a Hilbert envelope was derived yielding a timecourse showing fluctuations in the envelope of oscillatory power for each frequency band. These Hilbert envelopes were temporally smoothed (1s time resolution), and concatenated across subjects; the resulting dataset was analysed using temporal independent component analysis (ICA) to yield a set of 25 independent components per frequency band. The spatial signature of each temporal component (i.e. the maps in Fig. 1) was measured by Pearson correlation between the IC timecourse (extracted directly from ICA) and the timecourse of each voxel in the concatenated dataset. This process was implemented independently for each frequency band.

Quantitative comparison between RSN maps derived using MEG temporal ICA and RSN maps from spatial ICA in a previously published fMRI study11 was undertaken using a spatial correlation coefficient metric. The statistical significance of this correlation was measured using Monte Carlo simulations which take into account spatial bias in beamforming brought about by the non-uniqueness of the MEG inverse problem7.

Results: 8 RSNs’ spatial maps were unambiguously paired with RSNs derived from application of spatial ICA to resting state fMRI data11 and these are shown in Fig. 1 (upper panels show fMRI, lower panels show MEG). Fig. 1A shows the default mode network with MEG data filtered into the α (8-13Hz) band. Separate network nodes were observed in medial frontal cortex and the left/right inferior parietal lobules as expected. Fig. 1B (β band) shows a left lateralised frontoparietal (attention) network whilst Fig. 1C shows a right lateralised mirror image. These ‘attentional’ networks have been widely reported in fMRI studies and show compelling similarity across modalities with a similar left-right split. Figs. 1 D – H (β band) show MEG based temporal components originating in the sensori-motor network (D), the medial parietal region (E), the visual cortex (F), the medial frontal cortex (G) and the cerebellum (H). In all cases spatially independent fMRI components can be found that match significantly the spatial signature of a MEG component.

Discussion and Conclusion: The above results show that the spatial structure of multiple resting state networks, identified reliably by fMRI, can also be independently measured using MEG. This finding confirms an electrophysiological basis to these networks and supports recent work12,3,6 in showing that neural oscillations, particularly in the alpha and beta bands, play a role in network connectivity. The spatial resolution of fMRI is superior to that of MEG and this is clearly apparent from the results presented here. However, MEG offers a useful way to bypass the haemodynamic response and measure the electrophysiological basis of network activity and connectivity on a timescale relevant to brain function. It therefore follows that a multi-modal approach, using MEG and fMRI in conjunction, offers an excellent opportunity to study brain networks with high spatial and temporal precision. Work is currently underway to explore task-induced network changes using this methodology.


Acknowledgements: The Leverhulme Trust; Medical Research Council; Wellcome Trust; University of Nottingham.
Introduction: The study of functional brain networks is rapidly becoming an important area of neuroimaging. Many recent studies have employed fMRI to delineate a set of orthogonal brain networks, some associated with simple sensory processing (visual, auditory, motor etc.) and others associated with higher-level processes (e.g., the dorsal attention network, default mode network (DMN) and salience network). These networks are key to healthy brain function and disruption within these networks has been implicated in various pathological conditions. However, fMRI is limited since BOLD contrast is an in-direct measure of ‘brain activity’. Electrophysiological techniques that facilitate a more direct measure of neuronal activity and allow measurement of interactions on a finer temporal scale are increasingly being used to provide complementary information. Here, we investigate network changes during an N-back working memory paradigm. We use parallel BOLD and magnetoencephalography (MEG) (a modality that measures magnetic fields induced directly by synchronised neural current flow) experiments to assess the relationship between haemodynamic and electrodynamical measures of network activity.

Methods: Eight subjects took part in both the fMRI and MEG experiments. Paradigm: Participants performed an N-back working memory task. Each trial comprised 4 phases of working memory: 0-back, 1-back, 2-back, 3-back and a rest period. During N-back phases, letters were presented sequentially every 2 seconds and subjects executed a button press when the current letter presented matched that shown N letters previously. Each phase lasted 33/2s; the order of the phases was randomised across trials. 10 trials were recorded in fMRI and 12 in MEG. During rest phases, a fixation cross was presented. In addition, in the MR session a 5 minute resting state BOLD fMRI acquisition was also performed. fMRI acquisition: BOLD data were acquired using a 7T Philips system. GE-EPI comprising 24 contiguous slices (TR/TE 1500/25ms, 1.5x1.5x3mm resolution, 198x192 x2mm FOV, SENSE factor 3) were acquired giving whole brain coverage. Homogenous B0 was achieved using a paracollated shimming procedure. MEG acquisition: MEG data were acquired using a 275 channel system (600Hz sample rate). Co-registration of MEG sensor locations to anatomical MRI was achieved using head digitisation (Polhemus Isotrack). Data analysis: MEG data were filtered into frequency bands of interest and projected from sensor space to source space using a beamformer. For each voxel in source space, a Hilbert envelope was derived yielding a timecourse showing fluctuations in the envelope of oscillatory power for each frequency band. These envelopes were temporally smoothed (1s time resolution); concatenated across subjects; and analysed using temporal independent component analysis (ICA) yielding spatial maps corresponding to a set of electrodynamic brain networks. The raw MEG data were then used to reconstruct time-frequency spectrograms showing changes in oscillatory power across the whole network. MEG data were motion corrected, RETROICOR corrected and spatially smoothed (4mm Gaussian kernel). For the resting state data, a seed-based correlation analysis (seed region in posterior cingulate cortex (PCC) for default mode network (DMN)) was carried out to form spatial maps of the DMN. N-back data were analysed with a GLM, generating statistical maps of brain regions exhibiting significant signal change time-locked to the task. This thresholded (FWE p < 0.05) statistical map was masked with the DMN map from the seed-based correlation analysis to ensure that a common DMN ROI was formed for use in subsequent analyses. The BOLD signal change with respect to rest across the DMN was then calculated for each of the N-back task phases.

Results: Of a number of brain networks identified in both MEG and fMRI, here results focus on the DMN, which comprises medial frontal cortex, PCC and right/left lateral parietal cortices. Figure 1A shows the DMN identified using fMRI and Figure 1B shows its closest spatial match in MEG. Despite lower spatial resolution in MEG, three of the distinctive network nodes (medial frontal and left/right lateral parietal) are visible. Figure 1C shows the MEG time-frequency spectrogram, averaged across the DMN nodes for the 0-, 1-, 2-, and 3-back phases. Figure 1D shows the corresponding averaged BOLD timecourses. Note first that the mean BOLD amplitude reduction with task onset scales with increasing task difficulty (as indicated by N). In MEG, a similar scaling is observed with reductions in oscillatory power observed in the 13-40Hz range. However, note also that 13-40Hz power reductions are accompanied by concomitant increases in 4-8Hz (θ) oscillations. The mean change in oscillatory power (collapsed across the 13-70Hz band) for each phase is shown in Figure 1E, whilst Figure1F shows the equivalent % BOLD change, both showing power reductions scaling with 2-back phase. Finally Figure 1G shows BOLD signal change plotted against 13-70Hz changes for each N-back phase, with a degree of non-linearity observed, possibly reflecting BOLD saturation at high N.

Discussion and Conclusions: DMN activity has previously been characterised by high temporal correlations measured between network nodes during the resting state, and a decrease in BOLD amplitude during tasks. Here, in agreement with previous work, we show that BOLD signal amplitude and MEG β/γ band power decreases in the DMN during an N-back working memory task compared with rest. Also in-line with previous work, we show that the magnitude of these signal changes scales with task difficulty (N). This work shows a close coupling exists between BOLD signals and neural oscillations, within functionally relevant networks. Further, the results shown here are in close agreement with invasive electrophysiological recordings. The reduced spatial resolution associated with MEG is clearly apparent in the results shown. However, also apparent is the high time-frequency information content of MEG signals compared to BOLD. It therefore follows that a multi-modal approach to network measurements offers an excellent opportunity to study network behaviour with high spatial resolution and on a timescale relevant to brain function. As mentioned above, the DMN is only one of a number of networks identified as exhibiting spatial correlation across modalities. A multi-modal approach offers a promising way not only to understand functional connectivity between spatially distal network nodes, but also to probe the interactions between networks.


Acknowledgements: Medical Research Council; The Wellcome Trust; The Leverhulme Trust; The University of Nottingham.
INTRODUCTION: Conventional MRI sequences have limited sensitivity and specificity in diagnosing brain tumours. Extent of contrast enhancement does not correspond with the boundary of tumour cellularity which is critical when guiding maximal tumour resection and optimal radiotherapy target volumes. Previous studies have identified differences in diffusion patterns between tumour types however this has yet to be applied in clinical practice. We present a novel whole brain DTI k-means clustering algorithm that generates tumour diffusion maps. When this technique is applied to cases of intracranial mass lesions, resultant maps display distinctive patterns for each tumour type with visually delineated boundaries.

METHODS: MRI scans were acquired from 94 patients with suspected intracranial mass lesions: 11 meningioma (MEN), 26 metastases (MET), 31 spin-echo planar images (b=1000 s mm$^{-2}$) were acquired from 43 subjects using a 1.5T GE Signa LX (12 diffusion sensitised directions repeated 4 times) and 51 using a 1.5T GE Signa HD (61 diffusion gradient directions).

DTI segmentation technique: Histograms of $p$ and $q$ were computed across all brain voxels in all subjects simultaneously. High intensity noise was removed from the $p$ and $q$ distributions and all voxels above this threshold assigned to 1 and the remaining voxels scaled between 0 and 1. Initial cluster centroids were defined by separating $p$-$q$ space into equal quartiles (lower quartile, median and upper quartile, fig. 1A). Using a $k$-means clustering algorithm, each image voxel, $i$, was iteratively reclassified to one of 16 clusters based on the distance in ($p,q$) space of the voxel $(p_i,q_i)$ to its nearest cluster median $(m_{p,j},m_{q,j})$ by:

$$\min_{j \in \{1,2,\ldots,16\}} \bigg[ (p_i-m_{p,j})^2 + (q_i-m_{q,j})^2 \bigg].$$

This was repeated for 250 iterations with steady state of classification reached before termination (fig. 1B). $k=16$ was selected a priori to identify tissue classes present within the tumour-affected brain. Normal-appearing grey matter (NAGM), normal-appearing white matter (NAWM), cerebrospinal fluid (CSF), tumour mass (solid cellular component, necrosis, cyst and infiltrating margin), infiltrative peri-tumoural oedema and vasogenic oedema distant from the tumour.

Visualisation technique: $T_2$-weighted ($b=0$ s mm$^{-2}$) images were scaled between 0 and 1 on a subject-by-subject basis. Median values for each of the 16 cluster centroids for $p,q$ and $T_2$-value across the patient cohort were ranked (1 to 16). Rank scores were then assigned to the red channel ($T_2$-value), green channel ($p$) and blue channel ($q$) using a 24 bit RGB colour scheme. As the colour scheme is based on the ranks of the cluster centroids it is not affected by differences in magnitude between $p,q$ and $T_2$-weighted greyscale values. The colour key in fig 1D relates segment numbers to colours and cluster centroid ($p,q$) properties.

Segmented region of interest (ROI) delineation: Tumour regions were semi-automatically delineated from the segmented colour maps using a 4-voxel neighbourhood recursive flood-filling algorithm. This was performed on all axial slices containing tumour or oedema to generate a 3D tumour ROI. The percentage contribution of each segment within this tumour region was calculated. The mean percentage contribution of each segment was calculated for each tumour type. This was plotted graphically to generate tumour ‘spectra’ (fig 1E-H). A linear discriminant analysis (LDA) was performed to investigate which linear combinations of percentage contribution of each segment best discriminated between tumour types (fig 1C, colour key is shared with spectral graphs).

RESULTS: The technique generated colour maps with visually segmented boundary between tumour and normal brain with consistent colours for NAWM, NAGM and CSF spaces across subjects as well as tumour-specific colours. Example images are shown for each tumour type in fig 1 (LGG=1, GBM=2, cGBM=3, metastasis=4, meningioma=5). Spectral graphs allow comparison between tumour types (fig 1E-H). The salient results are as follows:

- Fig. 1E reveals increased cluster 12 in metastasis and increased cluster 8 in GBM. From the final Voronoi plot (fig 1B) and example images (fig 1: GBM and MET), it is evident this likely reflects different oedema characteristics between the tumours (vasogenic fluid-rich oedema metastasis v. infiltrative' cellular oedema in GBM).
- Greater proportion of clusters 7, 8, 9 and 10 are evident in GBM than LGG, which has increased proportion of cluster 13, fig.1F. This reflects greater tumour cell density in malignant gliomas (therefore lower isotropy than the diffuse cellularity in LGG).
- cGBM exhibit increased cluster 14 (fig. 1G) due to their constituent fluid compartment.
- Meningiomas have greater proportion of clusters 1-5 due to their densely packed, highly organised cellular microstructure (fig 1H).

The LDA (fig 1C) correctly classifies tumour type in 83 out of 94 cases (cross-validated post hoc), yielding diagnostic sensitivities of 83.9% GBM, 100% cGBM, 84.2% LGG, 72.7% meningioma and 92% metastasis with corresponding specificities of 95.5, 100, 94.9, 100 & 91.9%, respectively.

DISCUSSION: This is one of the largest studies to date of diffusion tensor imaging in brain tumour diagnosis. Our segmentation technique reveals improved diagnostic sensitivities and specificities than previously reported manual DTI-ROI drawing techniques for a greater range of tumour types. Combining clustered images with their corresponding Voronoi plot of $p,q$ space allows interpretation of regional diffusion characteristics and thus potentially tissue structure. Automatic tumour region of interesting techniques offer a fast, reproducible method of tumour diagnosis and may have a further role in delineating tumour regions for surgery and radiotherapy planning as well as the longitudinal surveillance of tumours pre or post treatment.

Calibration and Implementation of Quantitative Blood Oxygenation Measurement at 7T
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Introduction
A calibrated relationship between blood oxygenation and T2 has been exploited for quantitative measurement of cerebral venous oxygenation [1-4]. These methods have demonstrated potential utilities in normalization of fMRI signals [5], evaluation of brain metabolism [6], and understanding brain disorders [7]. To date, all such studies have been performed at the field strength of 3T or lower. Given the field dependence of deoxyhemoglobin susceptibility effects [8], it is reasonable to expect that a higher field, e.g. 7T, may provide a unique advantage in improving the sensitivity of this technique, in addition to the SNR increase that is common to all methods at 7T [9]. The goals of the present study are two-fold. First, we aim to establish a calibration plot between blood T2 and oxygenation at 7T (using in vivo blood sample experiment) in the context of various hematocrit levels (Hct). Second, we implemented a recently developed T2-Relaxation-Under-Spin-Tagging (TRUST) MRI technique [10] at 7T and determined venous blood T2 in vivo. Utilizing the calibration plot, human venous oxygenation was estimated and its response to hyperoxia maneuver was demonstrated.

Methods

In vitro blood experiments
In vitro experiments were performed on bovine blood samples in a 7T small animal MR scanner (Varian) with a 38 mm birdcage RF coil. The temperature of the blood sample was controlled by maintaining the ambient temperature of the magnet bore at 37°C. Experiments were performed on 7 batches of blood on separate days. Blood T2 at three Hct levels (Hct = .34, .42, .54) were assessed. At each Hct, the T2 dependence on oxygen saturation (Y) was examined. The blood T2 was measured with a CPMG multi-echo T2 sequence with (TECPMG = 5 ms). Estimation of T2 was based on standard mono-exponential fitting. The entire T2 data (all Y and Hct values) was fitted to a 3D plot using a mathematical model to determine the relationship between T2, Y and Hct.

In vivo human experiments
In vivo experiments were performed using TRUST at 7T (7T Philips Achieva, 16 Ch. Nova T/R volume headcoil). The TRUST technique applies the spin labeling principle on the venous side, and subtraction of control and labeled images yields pure venous blood signal. The T2 value of the pure venous blood is then determined using non-selective T2-preparation pulses, which minimizes the effect of flow on T2 estimation [10]. For implementation of TRUST at 7T, an adiabatic hyperboloid secant inversion pulse [11] was used for spin tagging (β = 400 rad/sec, μ = 8, FA = 1800, BW = 1020 Hz). To balance the magnetization transfer (MT) effect, an equivalent tagging pulse was played out below the imaging plane during the control acquisition. The T2-preparation incorporates hard composite pulses, MLEV-16 phase cycle, with (TECPMG = 5 ms). This results in a set of label and control images with three effective TE (TE = 0, 20, 40 ms). Due to short blood T2 at 7T, images were acquired with a multishot-EPi gradient echo (FOV = 220x220 mm2, matrix = 64x64, EPI factor = 3, 8 shots, SENSE factor = 3 (AP), TE = 2 ms, 1 slice, slice thickness = 5 mm). Six subjects (2 Female /4 Male) were scanned with TRUST to measure venous oxygenation in the superior sagittal sinus. The protocol for two subjects used recovery time (RT) of 9800 ms and inversion time (TI) of 1500 ms, where TR = RT + TI. All others were scanned with RT = 2500 ms, and TI between 600 and 900 ms.

Hyperoxia maneuver
To demonstrate the sensitivity of the technique in detecting oxygenation changes, an additional subject (1 Female) was scanned with 7T TRUST (RT = 2500 ms, TI = 700 ms) during normoxia and hyperoxia (98% O2, 2% CO2) conditions. After the scan, 5cc of blood was drawn from the subject’s arm to determine the Hct using a centrifuge. Venous oxygenation values under normoxia and hyperoxia were compared.

Results and Discussion
The in vitro blood data results are shown in Figure 1. As expected, the 7T blood T2 values are shorter than those measured at lower magnetic fields with the same T2CPMG (5 ms). For venous blood (Y=0.6) the T2 values of blood with Hct = 0.42 are 132 [12], 76 [13], and 20 ms [this study] for 1.5, 3, and 7T respectively. For arterial blood (Y = 1) the T2 values of blood with Hct = 0.42 are 193 [12], 164 [13], and 70 ms [this study] for 1.5, 3, and 7T respectively. A representative 7T TRUST data set is shown in Figure 2. The in vivo 7T data resulted in an average blood T2 value of 24.7 ± 4.1 ms in the sagittal sinus. Using the model of the in vitro blood data and assuming a Hct of .42, the in vivo blood T2 data can be converted to an average measured venous oxygen saturation of 64.8 ± 4.6 %. The T2 and calculated Y values for each subject lie within the expected physiologic range for venous blood. To test the sensitivity of TRUST at 7T, normoxia and hyperoxia conditions from one subject with Hct = 0.40 were compared. In normoxia, we measured T2 = 26.0 ms, which corresponds to Y = 65%. Hyperoxia resulted in T2 = 31.1 ms, which corresponds to Y = 70%. This increase in T2 and Y indicates the promising indication that TRUST at 7T is responsive to changes in blood oxygenation.

To the best of our knowledge, the present report is the first study to quantitatively estimate blood oxygenation at 7T. Our results provide a calibration plot for accurate conversion of blood T2 to oxygenation levels. Such data can be used to calibrate a number of venous oxygenation techniques including TRUST, QUIXOTIC [14], VSEAN [15], and others. Our in vivo results also demonstrate the feasibility of TRUST at 7T and provide a basis for further technical development of these methods at high field.

References

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Figure 1: In vitro blood T2 dependence on Y. (a) All blood data and fitted model. (b) 2D cross-sections of the model for each Hct.

Figure 2: 7T TRUST data, with Control and Label images, and the resulting Difference image for eTE = 0, 20, 40 ms.
Cerebrovascular reactivity in the brain white matter: magnitude, temporal delays, and age effects

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INTRODUCTION: Structural studies using T2w, DTI, and magnetization transfer have revealed a wealth of information about the brain’s white matter (WM) and its alteration due to aging and diseases. However, physiological properties of the WM are still poorly understood, partly due to limitations in SNR. Recent technical advances in several methodologies have provided the potential to examine vascular physiology in the WM (1, 4). We have recently demonstrated the feasibility of evaluating WM perfusion on a tract-by-tract basis and showed a strong relationship between WM perfusion and fractional anisotropy (FA) (2). The feasibility of the present study is to examine another important property of the WM microvasculature: its ability to dilate upon stimulation. This physiological property, known as Cerebrovascular Reactivity (CVR), forms the basis of the BOLD-response and is well understood in the gray matter (GM), but little is known about its characteristics in the WM. Note that vascular deficits in the WM may be responsible for many abnormalities observed on structural MRI (e.g. WM hyper-intensity, FA decrease) (3), and often precede these structural changes. In the present study, we used CO2 inhalation to determine CVR in the WM and compared it to that in the GM. The CVR responses were examined in the context of both amplitude and temporal shift. Age-related differences were investigated by including both younger and older participants. For completeness, baseline perfusion was also measured with ASL MRI.

METHODS: Experiment: 15 healthy young (27±5 years, age range: 20 to 35 years) and 15 healthy elderly volunteers (75±7 years, age range: 62 to 86 years) were recruited using criteria typical of normal aging. The participants had a minimal MMSE score of 26 and at least high school education. MRI was performed on a Philips 3T. For the CO2 inhalation test, the subject breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while single-shot BOLD EPI images (TE=35ms) were acquired continuously. This short-duration breathing paradigm has previously been shown to improve subject comfort yet maintaining data quality (4, 5). End-tidal CO2 (Etco2), the CO2 concentration in the lung and thus arterial blood, is recorded throughout the breathing task and a regional time-course, which is a linear combination between the Etco2 signal and the WM time course yields the CVR value in the unit of %BOLD/mmHg. For comparison, baseline cerebral blood flow (CBF) was measured using pseudocontinuous ASL and absolute CBF (in ml/100g/min) was quantified with an approach described previously (6). An MPRAE image (resolution 1x1x1 mm³) was also acquired for anatomic reference and for GM/WM segmentation. Data Analysis: Only ROI analysis was performed and no attempt was made for voxel-wise analysis, as the low sensitivity in WM (which contains 75% less blood compared to GM) precludes a reliable measurement on a voxel level. Extreme caution was taken to avoid any GM contribution in the WM ROI: BOLD EPI images were co-registered to the MPRAE scan; an MPRAE-derived WM mask (thresholded at 90% WM probability) was obtained. Recognizing that the BOLD resolution (3.4x3.4x5.5 mm³) is considerably lower than MPRAE and that there could be slight misregistration between BOLD and MPRAE, we further eroded the WM mask three-dimensionally by six times (peeling off a 1mm layer each time), resulting in a rather small but minimally contaminated WM ROI. BOLD time-courses of the voxels within the ROI were subsequently averaged. From the averaged BOLD time-course, two measures were obtained: the temporal shift and the response amplitude. Previous studies have established that the trace of end-tidal CO2 and GM BOLD signal have a time shift of ~15 sec (4), which is the total time it takes for the blood to travel from the lungs to the brain tissue and for the vessels in the tissue to react to the change in CO2-concentration. This delay time is expected to be greater for WM, and was determined by shifting the traces relative to each other until maximal Cross-Correlation (CC) was observed. Next, the response amplitude was calculated using a linear regression between the WM BOLD time-course and the shifted end-tidal CO2 trace. A GM ROI was also identified from a single slice above the lateral ventricles. The BOLD time-course was extracted and the measures of temporal shift and response amplitude were calculated using procedures similar to those for the WM. GM samples from other regions and slices were also investigated, but no dependency of the results on sampling position was found. From the ASL data, baseline CBF was obtained for both GM and WM ROIs.

RESULTS and DISCUSSION: Averaged traces of Etco2, GM and WM BOLD time-courses are shown in Fig. 1. A clear temporal delay in the WM time-course can be observed relative to the GM. Table 1 summarizes CVR results for both young and old subjects. It can be seen that the BOLD response in the WM occurs as late as 21 seconds after the GM response. This is surprising considering that the WM ROI is just a few centimeters deeper located than the GM. Of course, it is well known that blood arrives later in the WM than the GM due to the known layout of the vasculature. However, evidence from ASL and DSC-MRI literature suggests that this should only be 2-3 seconds at most (7). Therefore, we could only speculate that this large delay is primarily due to a delayed reaction time of the WM vasculature compared to the GM. Elderly individuals manifested a smaller GM/WM time delay (Table 1), but the delay was nonetheless on the order of 10 seconds. For CVR amplitude, GM CVR showed an age-related decrease, consistent with the expected age effect and previous reports (5). WM CVR, on the other hand, was higher in the older subjects. Baseline CBF manifested similar patterns (Table 2): GM CBF was significantly higher in younger participants, whereas there was a trend for a higher WM CBF in the older participants. The present study provided an unprecedented examination of cerebrovascular reactivity in the WM and its dependence on age. Our data suggested that vascular physiology in the WM is drastically different from that in the GM. Specifically, blood flow and reactivity decrease with age in the GM (which is more in line with traditional thoughts), but the opposite pattern is seen in the WM. We hypothesize that this may be associated with the unique mechanical properties of the WM. WM in young subjects is tightly packed with axons and myelin, which makes it difficult for blood to penetrate and for vessels to dilate. In older individuals, as age-related demyelination and axon loss takes place, WM becomes less densely packed, thus exhibiting less hindrance for blood to flow through loose white matter fibers. We also observed a surprisingly large difference between the GM and WM response time, which we have no clear explanation for at this point.


Table 1. CVR results

<table>
<thead>
<tr>
<th></th>
<th>GM (% BOLD/mmHgCO2)</th>
<th>WM (% BOLD/mmHgCO2)</th>
<th>GM to WM delay (s)</th>
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<tr>
<td>young</td>
<td>0.265 ± 0.051</td>
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<td>20.8 ± 9.25</td>
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<tr>
<td>old</td>
<td>0.231 ± 0.045</td>
<td>0.061 ± 0.018</td>
<td>12.26 ± 4.89</td>
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<td>p-value</td>
<td>0.005</td>
<td>0.048</td>
<td>0.003</td>
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</table>

Table 2. Baseline CBF results

<table>
<thead>
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<th></th>
<th>GM (mL/100g/min)</th>
<th>WM (mL/100g/min)</th>
</tr>
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<tbody>
<tr>
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<td>82.88 ± 11.57</td>
<td>20.36 ± 3.71</td>
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<tr>
<td>old</td>
<td>69.29 ± 9.24</td>
<td>24.21 ± 7.10</td>
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<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.072</td>
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MR Fingerprinting (MRF): a Novel Quantitative Approach to MRI

Introduction: Conventional MRI attempts to generate pure “weighted” images that depend only on one or two parameters of interest. Much of the MR pulse sequence development at ISMRM is directed at generating a constant signal level over time to acquire a weighted image as quickly as possible. It is well known that this is difficult to achieve (e.g. pure T2 weighting in a fast spin echo sequence) and is limited in the presence of motion or phase changes. Here we propose a new concept for MRI based on recent advances in Compressed Sensing which we call MR fingerprinting (MRF). MRF is based on a change in perspective: instead of providing a constant signal level over time, we use a sequence that attempts to generate a different signal evolution for each tissue with different relaxation parameters. We then use a pattern recognition based reconstruction to derive quantitative estimates of the underlying relaxation parameters. This is analogous to matching fingerprints (MR signal) to a database (dictionary), and by extension retrieving a host of additional personal information such as identity, address, phone number, etc. (T1, T2, diffusion coefficient, etc.). Here we show that these estimates are independent of B0 and B1 variations using a sequence with very low SAR. We initially demonstrate this MRF concept by generating quantitative MR images in a clinically feasible time.

Methods: The goal of an MRF sequence is to provide a unique signal evolution in each tissue type by varying the basic sequence parameters. One example of this type of sequence is to use random TrueFISP, which was chosen for the first demonstration of MRF due to extensive existing knowledge about the evolution of the TrueFISP signal evolution. Figure 1 demonstrates a sequence where 500 data points for each pixel were acquired. For each data point, we randomly varied the TR (range: 6.6-10ms) and flip angle (range: 2-6 degrees), and an inversion pulse was added every 200 TRs. Using such a sequence, the signal varies wildly from one TR to the next (see Figure 1C). To determine the relaxation parameters, pattern recognition of the signal time course is completed using Orthogonal Matching Pursuit (OMP) [2,3], which can resolve the correct signal and obtain multiple parameters simultaneously. OMP involves building a dictionary that contains all expected signal evolutions based on the designed sequence parameters (TR, TE, flip angle, B0) by using a Bloch simulation. This method was evaluated in a phantom study, where 10 cylindrical phantoms constructed with varying concentrations of GadCl3 (Aldrich) and agarose (Sigma) to yield T1 and T2 values ranging from 67 to 1700 ms and 30 to 300 ms, respectively. The phantom was scanned using a 1.5T Siemens Espree (Siemens Medical Solutions). Around 15000 characteristic parameter sets (T1 from 50 to 2000 ms, T2 from 20 to 400 ms, and off-resonance from -40 to 40Hz) were used to simulate possible signal time courses using Bloch simulations of the spin evolution, and were stored in the dictionary. OMP was then used to select the elements from the dictionary that best represent the acquired signals, yielding the corresponding T1, T2, proton density, and off-resonance maps. As a gold standard comparison, a standard spin-echo sequence was performed to quantify T1 and T2 separately (T1 quantification: 13 TRs ranging from 50 to 5000ms, TE = 8.5 ms; T2 quantification: 15 echoes with TE=15-225 ms with 15ms increment). T1 and T2 maps of the spin echo sequences were obtained by fitting the time courses on a pixel-by-pixel basis using a three-parameter nonlinear least squares fit. Square regions of interest (ROI) were chosen from each of the cylinders and the mean MRF values were compared with the values from the standard measurements.

Results and Discussion: Figure 1C shows the signal time course from one pixel of the reconstructed MRF series and its corresponding dictionary match. The T1, T2, M0, and off-resonance maps generated from MRF are shown in Figure 2. In Figure 3, T1 and T2 values obtained from MRF methods are compared with the values from standard spin-echo sequence measurements. As can be seen in Figure 3, both T1 and T2 values are in good agreement with the traditional measurement even though the MRF sequence used only very low flip angles. In addition, we simultaneously obtained a map of off-resonance. The concept of MRF uses a completely different approach to experimental design in MRI, where the sequence design is optimized not towards yielding individual images with various weightings, but rather towards generating unique signal timecourses that can be matched with a compressed sensing approach to the corresponding parameters to yield the underlying tissue parameters. The method is robust as long as the designed sequence provides unique signal evolution curves for different tissues, and the chosen reconstruction method is able to generate the required parameter maps. In addition, because a single preparation is avoided, the equilibrium signal state is never reached, which allows for continuous scanning to assess measure multiple parameters at once. Also, since the reconstruction is probabilistic, MRF may be less susceptible to motion. The presented sequence design is but one of the infinite sequence designs possible and to be explored, that could yield quantification of any of the various parameters which affect the MR signal without errors due to B0, B1, and other effects.

Whole-brain DSI in 4 minutes: sparse sampling in q-space with simultaneous multi-slice acquisition

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Introduction: High angular resolution diffusion imaging (HARDI) techniques (1-3) have been developed to provide robust and detailed information about the local diffusion encoding in the brain white matter, particularly in regions of crossing fibers. A drawback of these techniques is their requirement for a large number of diffusion encoded acquisitions with strong diffusion encoding which can lead to slow SNR and lengthy acquisitions. This is particularly true for DSI (2) where a 515 direction whole brain scan takes an hour or longer, limiting its utility in clinical and research studies. In this work, we aim to significantly improve the efficiency of HARDI acquisitions using three orthogonal, beneficial technologies: (i) high strength gradient hardware, (ii) Simultaneous Multi-Slice (SMS) acquisition with Blipped-CAIPI acquisition scheme (4) with a highly parallelized reception coil array, and (iii) q-space compressed sensing reconstruction (5). Together, these improvements allow for an acquisition of high-quality whole-brain DSI data in just 4 minutes. While this initial demonstration focuses on DSI, the general approach should be applicable to other HARDI acquisition schemes.

Methods: Stejskal-Tanner based diffusion EPI acquisitions were obtained from a healthy volunteer using a novel 3T system (MAGNETOM Skyra CONNECTOM®, Siemens Healthcare, Erlangen, Germany) equipped with the AS302 “Connectom” gradient with Gmax=300 mT/m and slew=200 T/m/s. A custom-built 64-channel RF head array (6) was used for reception. A 3x slice-accelerated SMS acquisition with Blipped-CAIPI acquisition scheme was used to reduce the acquisition time 3-fold. Here, a FOV/2 inter-slice image shift between the 3 simultaneously excited slices was utilized to reduce the g-factor penalty (we previously demonstrated <5% penalty at this slice acceleration factor with a 32 channel array (4)). Imaging parameters for the 3xSMS accelerated acquisition were: 2.5mm isotropic; FOV = 210 x 210 x 130 mm; Partial Fourier = 6/8; matrix size = 84x65x17; bmax = 8000 s/mm², 515 directions full sphere q space sampling on 11x11x11 grid, TR/TE = 1.9s/72 ms, total image time ~16 min. The max gradient strength for this preliminary acquisition was limited to 100 mT/m to reduce eddy current distortions. To minimize aliasing artifacts, slice-GRAPPA (4) with modified even/odd grappa kernel (7) was used to reconstruct the slice collapsed dataset. Optimal coil combination was performed to provide improved SNR and mitigate the non-central Chi-squared noise bias (8) of the root sum of square (rSOS) reconstruction. Eddy current related distortion and subject motion was corrected using a modified eddy_correct function in the FMRIB’s diffusion toolbox (9) with sinc interpolation.

A 4x undersampling of the reconstructed 515 directions full sphere q-space dataset was then performed using a 2x-avg Gaussian undersampling scheme on a half sphere (with full sampling in the central q space region and increasing undersampling as a function of radius). The resulting dataset corresponded to 4 min of DSI data acquisition. To fill in the missing q-space directions of this data, the FOCUSSS compress sensing algorithm (10) and conjugate symmetry assumption of q-space were utilized. Here a t constraint on the probability distribution function (pdf) was used. For both the 3xSMS+1xQspace (16 min) and the 3xSMS+4xQspace (4 min) accelerated acquisitions, the pdf and ofd were estimated and tractography was conducted and compared using the Diffusion Toolkit (11).

Results: Fig1 left shows the aliased images from a selected group of 3xSMS slices at b = 0 and 8000 s/mm² (top and bottom respectively). Here, the collapsed images were reconstructed using rSOS coil combination resulting in a strong non-zero mean noise bias in the b = 8k image that obscures some image features. Fig1 right: shows the unaliased and optimally coil combined images of the same b = 8k acquisition illustrating that relatively high SNR and contrast that can be obtained in a single shot at b = 8000s/mm². The g-factor penalty for this 3x-slice accelerated acquisition is negligible but the TR reduction from 5.7s to 1.9s (allowed by the SMS acquisition) results in a T1 recovery related SNR loss of 14.6% per shot (WM T1 ~1s) but a net gain in SNR per unit time of 48%. On a standard gradient coil (Gmax: 40 mT/m) with no slice acceleration, the 515 DSI acquisition would have had a TR/TE of 8s/112ms and taken 1 hr and 10 min to acquire. The TE increase from 72ms to 112ms would have resulted in an SNR reduction of 44% (WM T1 ~70ms). To match the SNR of the standard acquisition to our 16 min scan, 2.3x averaging would be required to counteract this SNR loss (45% net SNR gain), resulting in a 2 hr and 40 min scan. Fig2 shows a comparison of the tractography results obtained from 3xSMS + fully sampled q-space (16 min) and 3xSMS + 4x undersampled q-space (4min) acquisitions. The tracts from both datasets clearly depict the fiber crossing regions, with minor additional noisy tracks in the 4 min dataset. Also shown are the diffusion images of the missing q-space directions at b= 4500 and 7000 s/mm² (top and bottom respectively). It can be seen that application of q-space compressed sensing algorithm at a per voxel level results in good reconstruction of the images of these missing directions with close resemblance to the ‘ground truth’ image of the 1x q-space data. We note that at very high b-values the compressed sensing reconstruction produces images that are somewhat nosier and lower intensity when compared to the ‘ground truth’ data (as can be seen in b=7k in Fig2). This is most prominent at the maximal b=8k. To overcome this, our undersampling scheme was modified to keep all of the b=8k directions on the half sphere, resulting in an increased acq time of 17s. Fig3 shows additional tractography results from the 4 min acquisition where detailed fiber structures can be observed.

Simultaneous OEF and Haematocrit assessment using T2 Prepared Blood Relaxation Imaging with Inversion Recovery

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INTRODUCTION: Oxygen metabolism and the bloods degree of oxygen saturation are important parameters not only for the evaluation of patients such as stroke or apnea but also within neurosciences. Here, information about the oxygen extraction fraction (OEF) is important for the interpretation of the blood oxygenation level dependent effect. Techniques such as TRUST [1] have been developed for measuring T2 of the venous blood and by using a prior known relationship between T2 and the oxygen saturation (Y) the global OEF can be calculated. One caveat of this method is the fact that the T2 versus Y relationship depends on haematocrit (Htc) [2], a parameter which is not always available. In addition, bloods T1 depends on haematocrit [3] and this has implications for perfusion quantification using Arterial Spin Labeling (ASL) which is also an important part in the nutritive supply and metabolism assessment of the brain. In healthy volunteers and most patients under normal conditions, a relative normal OEF and Htc can be assumed. This is however not the case in e.g. the neonatal population, where Htc often is outside the normal adult range (38-46%) [4]. Large variations in the arterial oxygen saturation can also be observed and need to be taken into account when estimating the OEF. Another group is cancer patients undergoing radio- and chemotherapy which can result in altered haematocrit.

In this work we present a robust method which simultaneously measures T1 and T2 of the venous blood using a “T2 Prepared Tissue Relaxation Inversion Recovery” (T2-TRIR) sequence from where both OEF and haematocrit can be estimated.

METHODS: The T2-TRIR sequence is shown in Fig. 1. In brief, it presaturates the image region (Fig. 2b) after which the longitudinal magnetization is T2 prepared using a standard MLEV preparation [1]. Subsequently, an inversion pulse is applied (Fig. 2b) and multiple readouts at flip angles large enough to saturate the surrounding tissue are performed. The inversion recovery of venous blood, entering the image slice from the superior part of the sagittal sinus, can thereby be measured. The sequence is repeated in groups of 4, each with an effective MLEV TE preparation of 0, 40, 80 or 160 ms. This corresponds to 0, 4, 8 and 16 refocusing pulses using an interpulse time (t_{interp}) of 10 ms. In this work the sequence is used for measuring bloods T1 and T2, however the technique works equally well for simultaneous T1 and T2 mapping in tissue, as long as a low flip angle Look-Locker readout is used instead.

For fitting bloods T1b and T2b, the signal from the four inversion recovery curves (Fig. 2a) were fitted simultaneously using:

\[ M_s(T1) = M_{eq}[1-(1.0+c/(1+e^{-TE/\text{IE}}))] \]

where T1 is the inversion times, \( M_{eq} \) is bloods equilibrium magnetization, c,TE, the effective MLEV echo time, and IE is the inversion efficiency. Magnetization is allowed to fully recover into a haematocrit of 43%, a venous oxygen saturation of 59% and an oxygen extraction fraction of 40%.

Four healthy volunteers and 5 neonates were scanned (3T Philips Achieva) using T2-TRIR according to institutional guidelines. The scan parameters were: TR/TE/\( \Delta T1\)/T1=15000/20/150/130 ms, phases=60 160x160 matrix, FOV=240x240 or 160x160 for neonates, flip-angle=95°, 2mm slice, SENSE=2.5 and eTE=0,40,80 and 160ms. Total scan time 2:15.

RESULTS AND DISCUSSION: Figure 2a shows an example fit to a single voxel in the sagittal sinus, typically 5-10 voxels are averaged for the final result. The region of interest is automatically extracted (Fig.2c) and the least noisy fits from within that region are chosen. Table 1 shows the corresponding T1, T2, Htc and OEF estimated from the healthy volunteers as well as the neonates. Oxygen saturation using pulse oximetry and Htc from blood samples was also available in some of the neonates. The observed values are in line with literature values and separate T1 and T2 mapping using the techniques from [1] and [3] (data not shown), indicating that robust T1 and T2 mapping in blood is possible within 2:15 min. This is crucial for perfusion estimation using ASL in neonates and possibly cancer patients, while at the same time gathering information about the global OEF. Global metabolic rate of oxygen can be estimated by combining the technique with full brain ASL or velocity mapping of the feeding vessels.

CONCLUSION: A robust T1 and T2 tissue mapping method has been developed and when applied on the venous blood it allows for non-invasive assessment of both haematocrit and OEF simultaneously. Further validation work is ongoing in healthy subjects using a reactivity challenge as well as in neonates where it is compared to near infrared spectroscopy and blood drawn haematocrit. However these initial results puy up and blood drawn haematocrit in neonates as compared to adults which necessitates mapping of bloods T1 e.g. to correct cerebral blood flow quantification using ASL or for calibrating the OEF estimate.


ACKNOWLEDGEMENT: This research is supported by the Dutch Technology Foundation STW, applied science division of NWO and the Technology Program of the Ministry of Economic Affairs as well as the ZonMW Electromagnetic Fields and Health program.

Figure 1. Sequence for simultaneous T1 and T2 blood measurements. The sequence is repeated 4 times, each with a different T2-preparation, resulting in effective TEs of 0,40,80 and 160ms.After the T2-prep, inversion of the blood in the sagittal sinus region followed by multiple readouts allows acquisition of four different inversion recovery curves from where venous blood T1 and T2 can be estimated.

Figure 2. a) Single voxel example fit to the four inversion recovery curves with effective echo times of 0,40,80 and 160ms respectively. The difference in T2 preparation gives rise to four sufficiently different recovery curves which allows for robust fitting of both T1 and T2 simultaneously. The blood inversion recovery arises from the inversion of venous blood, while sampling at multiple inversion times (b). Repeated and appropriately spaced acquisition at a high flip angle ensures saturation of surrounding tissue while allowing only “fresh” blood to be imaged. Automatic localization of the sagittal sinus (c) can be done using the later phases where blood signal is high and static tissue suppressed. The current fit results in a T1 of 1.71s, T2 of 56ms which can be translated into a haematocrit of 43%, a venous oxygen saturation of 59% and an oxygen extraction fraction of 40%.

Table 1 (H=Healthy Adult, N=Neonatal Patient. Values in brackets were assumed)

<table>
<thead>
<tr>
<th>Subject</th>
<th>T1 [s]</th>
<th>T2 [ms]</th>
<th>T1-Htc [%]</th>
<th>Htc [%]</th>
<th>OxySat. [%]</th>
<th>OEF [%]</th>
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<tr>
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<td>63</td>
<td>47</td>
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<td>(98)</td>
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<td>43</td>
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<td>45</td>
<td>-</td>
<td>(98)</td>
<td>37</td>
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ACKNOWLEDGEMENT: This research is supported by the Dutch Technology Foundation STW, applied science division of NWO and the Technology Program of the Ministry of Economic Affairs as well as the ZonMW Electromagnetic Fields and Health program.
Disentangling contributions from iron and myelin architecture to brain tissue magnetic susceptibility by using Quantitative Susceptibility Mapping (QSM)

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INTRODUCTION – Magnetic susceptibility is an intrinsic physical tissue property which recently became accessible in vivo by a novel imaging technique called quantitative susceptibility mapping (QSM) [1,2]. Susceptibility maps of the human brain demonstrate astounding anatomical contrast [1,2], which is currently believed to be predominantly due to iron (paramagnetic) and myelin-lipids (diamagnetic) [3]. The intermixing of both contributions, however, complicates interpretation of susceptibility changes in particular in neurodegenerative diseases where inflammatory myelin-loss and focal iron accumulation may occur simultaneously. It has, furthermore, recently been discovered that a considerable orientation dependence of brain tissue susceptibility exists, which further complicates interpretation. We present a novel technique for substantially increasing the specificity of QSM by utilizing additional R* information. The technique yields two novel contrasts, one that is independent of orientation effects, whereas the other is independent of tissue iron concentration.

THEORY – A three compartment tissue model was assumed with punctuate particle inclusions (called iron in the following) and myelinated axons in a homogenous tissue matrix. In this model, the bulk voxel susceptibility can be expressed by Eq. 1 (volume fraction of iron neglected) [1]. The corresponding relation for the effective transverse relaxation rate, R*, is given by Eq. 2 [4,5]. In both equations the terms associated with myelin depend on the orientation of the axons relative to the main magnetic field (angle \( \theta \)) as described by Eq. 3 [5] and Eq. 4 [6,7]. The dependence on iron concentration can be eliminated from the equations by linear combination of Eq. 1 and Eq. 2 according to Eq. 5, yielding a novel iron-independent contrast \( \xi_{\text{noFe}} \). The coefficient \( \hat{\xi}_{\text{noFe}} \) can be estimated from literature values (this study; see Tab. 2) or from R* and susceptibility values in regions with a similar contribution of myelin. The contrast \( \xi_{\text{noOrient}} \) depends linearly on the myelin-lipid volume fraction and includes the myelin-related orientation dependencies. A rotation invariant contrast may be generated by a linear combination of Eqs. 1 and 2 that eliminates the \( \theta \)-terms according to Eq. 6. This contrast is linear with respect to both the iron concentration and the myelin volume fraction.

MATERIALS AND METHODS – To demonstrate the technique, high-resolution double-echo GRE data was acquired from the brain of a volunteer (male, 26y) using the ToF-SWI-sequence [9] (TE/TE\textsuperscript{iso} = 3.83ms/22ms, TR = 30ms, FA = 20°, 600µm voxels; acquisition time: 15min.) on a 3 Tesla whole-body MRI scanner (Tim Trio, Siemens Medical Solutions, Erlangen, Germany) using a 12-channel receive head-matrix coil. The scan was repeated with the volunteer’s head in head-nodding position to investigate orientation effects. The resulting complex-valued images were registered to the normal head position using FSL-FLIRT (FMRIB, Oxford University). R* maps were computed from the magnitude echoes with compensation of Rician noise [10] and susceptibility maps were reconstructed from the phase images using the HEIDI algorithm [submitted to ISMRM]. The maps were, finally, combined according to Eqs. 5 and 6. The unknown constant \( \hat{\xi}_{\text{noOrient}} \) in Eq. 6 was determined by minimizing the difference between the orientation independent contrasts, \( \xi_{\text{noOrient}} \), of the two head orientations (A,B) in the corpus callosum: \( \text{min}_{\hat{\xi}_{\text{noOrient}}} \left[ \| \hat{\xi}_{\text{noOrient}} - \hat{\xi}_{\text{noOrient}} \|_2 \right] \). RESULTS – The experimentally determined value of \( \hat{\xi}_{\text{noOrient}} \) was \( (7.9 \pm 0.4) \text{ ppm/Hz} \). Figure 1 depicts R* maps and susceptibility maps as well as the two new contrasts. The R* and susceptibility maps demonstrate substantial different contrast in the region of the corpus callosum (arrows) due to anisotropic magnetic properties of myelin (Eqs. 3 and 4). This orientation dependence is also present in the new iron-independent contrast, \( \xi_{\text{noOrient}} \), which, furthermore, delineates cortical gray matter supporting recent results that attribute the susceptibility contrast between cortex and gray matter to different myelin content [1,3]. The orientation independent contrast, \( \xi_{\text{noOrient}} \), was relatively homogeneous compared to the other contrasts and demonstrated only minor intensity variations between the two head orientations which may be attributed to inaccurate QSM or R* reconstruction. Figure 2 shows slices of the basal ganglia region. Iron laden nuclei were discernable only in the \( \xi_{\text{noOrient}} \) images (square-ended arrows) while major fiber tracts were delineated predominantly in the \( \xi_{\text{noOrient}} \) images (straight arrows).

DISCUSSION AND CONCLUSIONS – The proposed technique disentangles magnetic properties related to punctuate susceptibility inclusions and myelin architecture using magnitude and phase signal of a clinically established GRE sequence. The coefficient \( \hat{\xi}_{\text{noOrient}} \) in Eq. 5 is independent of the magnetic moment of the particles [11]. Variations in the iron-independent contrast, \( \xi_{\text{noOrient}} \), therefore, cannot be attributed to any type of punctate paramagnetic inclusions, such as ferritin cores or transferrin molecules. The technique, thus, provides a unique means for specifically investigating the contentious biophysical source of pathological tissue susceptibility variations in vivo, e.g., in white-matter lesions of multiple sclerosis patients. The orientation-independent contrast, \( \xi_{\text{noOrient}} \), represents a mixture of contributions from iron and myelin. It may, however, be supposed that \( \xi_{\text{noOrient}} \) is relatively insensitive to variations of myelin content, because the value of \( \hat{\xi}_{\text{noOrient}} \) has recently been shown to be similar to the matrix susceptibility [6]. Future studies will involve post-mortem experiments for thoroughly investigating the specificity and sensitivity of the proposed technique.


Table 1. Encoded values. Variables are explained in Table 2.

![Figure 1](image1.jpg)

**Figure 1.** Input data (R*, QSM) and novel contrasts (\( \xi_{\text{noFe}}, \xi_{\text{noOrient}} \)) with the volunteer’s head in two different orientations (top and bottom). The arrows point to considerable orientation dependent contrast in the input datasets.

![Figure 2](image2.jpg)

**Figure 2.** Novel contrast in the iron-laden basal ganglia region (normal head position). Straight arrows mark orientation dependent myelin contrast (left only). Square-ended arrows mark contrast due to iron (right only).
Enhanced fMRI Sensitivity using CBV based Contrast with the Blood Pool USPIO Agent Ferumoxytol in Humans
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Introduction: Functional MRI (fMRI) has commonly been performed using BOLD (Blood oxygenation level dependent) technique, which depends on complex interactions between multiple physiological processes and has inherent resolution limits due to sensitivity to large veins. Animal studies have shown that contrast agent based blood volume functional MRI (fBVI) technique using blood pool iron oxide contrast agent promises significantly improved contrast to noise ratio (CNR) [1]. fBVI therefore could allow mapping of brain function at high spatial resolution. This technique was however not possible until recently due to the lack of blood pool USPIO (ultrasmall superparamagnetic iron oxide) suitable for human use. Here we report the first study of the use of USPIO (ferumoxytol, AMAG Pharmaceuticals, Inc., Cambridge, MA) for fMRI in humans.

Materials and Methods: The study was approved by the local Institutional Review Board. MR imaging was performed at 3T with an 8-channel head coil (MR750, GE Healthcare, Waukesha, WI). Four subjects were scanned with the following protocol: A 3D T1-weighted inversion recovery spoiled gradient echo (IR-SPGR) sequence covering the entire brain was acquired. BOLD fMRI and fBVI were performed using a 2D gradient echo EPI sequence before and after the injection of ferumoxytol (approx 7 mg Fe/kg) respectively (FOV=22cm, Matrix = 64x64, slice thickness = 4, number of slices = 36, TR=2s). The echo time (TE) was 35ms for pre-contrast BOLD, and both 20ms and 35ms were used for fBVI to explore the optimal TE for fBVI. The subjects performed 4 epochs of 48s of right hand finger tapping and 48s of rest. The fMRI images were processed using SPM8 and custom MATLAB scripts. They were registered to correct for motion and smoothed with a Gaussian kernel with a full-width half height of 7mm. The General Linear Model was used to identify region of activation. Time courses from the activated region in the motor area were extracted and analyzed using both mono- or bi-exponential response models to obtain a time constant (Tc) which characterizes the speed of BOLD fMRI and fBVI signal to stimulus (larger Tc indicates slower responses). The relative sensitivity of BOLD fMRI and fBVI were compared using CNR ratio and Student’s T statistics. CNR ratio was calculated as the ratio between the standard deviation of fitted signal time course between fBVI and BOLD fMRI.

Results: A mono-exponential model provided a good fit for the BOLD fMRI time course with mean (std) Tc of 6.7(1.6s). For fBVI, both a slow and a fast component were found. The mean(std) Tc for the slow and fast components was 72.5(14.2)s, and 6.2(2.3)s, respectively. The normalized coefficient was defined as the ratio between the fitted coefficient and the sum of the coefficients of the two exponential components. And the mean (std) value of the normalized coefficient for the slower components was 0.097 (0.043). For fBVI with TE = 20ms, the mean CNR gain over BOLD was 2.5, ranging among subjects between 2 and 2.9 (Fig 1); while for TE=35ms, the average gain was 1.5. This CNR gain was reflected as higher student’s T statistics in the activation map (Fig 2).

Discussion and Conclusion: To our knowledge, this is the first study on the use of USPIO as contrast agent for improved fMRI sensitivity in humans. The signal contrast of fBVI is primarily CBV based. This study shows that fBVI signal contains both a fast and a slow component, which may correspond to arteriolar and venular sources respectively [2]. fBVI fMRI has a CNR gain of a factor of 2 to 2.9 over BOLD fMRI. This CNR gain results in higher but non-proportional gain in T-statistics, as physiological noise is the primary source of noise at the current resolution. The CNR gain may be more effectively used to invest in high-resolution fMRI studies [3]. In conclusion, fBVI substantially improves the CNR for activation detection, and opens the possibilities of high-resolution fMRI at 3T, such as mapping of human ocular orientation columns [4].


Acknowledgements: National Institute of Health (2R01NS047607, 1R01NS066506, SP41RR09784), Lucas Foundation and Oak Foundation.
**Functional MRI with SWIFT**

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**Introduction**

Despite the large utilization of the Blood Oxygenation Level Dependent (BOLD) contrast [1], intense theoretical and experimental efforts are currently devoted to design novel methodologies for fMRI in an effort to more directly access cellular (rather than hemodynamic/metabolic) events. Available models predict that the BOLD signal change approaches zero when data acquired at different echo times (TE) are extrapolated to TE=0 [2]. This implies that a technique which generates no echo has the potential to detect phenomena other than T₂ or T₂⁺ changes related to deoxyhemoglobin (dHb). Here, we applied in fMRI a novel methodology, sweep imaging with Fourier transformation (SWIFT) [3], which provides 3D coverage of the brain in a few seconds without producing an echo. Also, since SWIFT is a 3D method, the inflowing blood signal can be minimized when using a volume coil. SWIFT is also compelling for fMRI applications because it drastically minimizes the acoustic noise associated with the scanning procedure. We performed experiments on the human brain at 4 T during visual stimulation. In addition, with the goal of characterizing the origin of the SWIFT functional contrast, we performed experiments on the rat brain during respiratory challenges and on phantoms containing arterial or venous blood at 9.4 T.

**Methods**

Four healthy subjects were scanned at 4 T. One-hundred 3D-SWIFT volumes were acquired with TR=1.5 ms, flip angle=3°, spatial resolution=2.7 mm (isotropic), temporal resolution=5.2 s. For anatomical reference, T₁-weighted images were collected with MPRAGE (spatial resolution=2x1x2 mm³). The functional protocol consisted of a block-design paradigm (20 off–20 on–20 off–20 on–20 off), employing a radial red/black checkerboard flickering at 8 Hz and covering the entire visual field. One rat was scanned at 9.4 T. One-hundred 3D-SWIFT volumes were acquired with TR=1.5 ms, flip angle=2°, spatial resolution=0.5 x 0.5 x 2 mm³, temporal resolution=3 s. At scan #20 and #60 the ventilator for the animal was switched off for 20 s. Finally, SWIFT and gradient echo (GRE) images were acquired on a phantom containing two 5-mm tubes filled with arterial or venous blood obtained from a rat.

**Results and Discussion**

Robust activation during a visual stimulation paradigm was detected over the primary visual cortex including the gray matter areas (Fig. 1). The signal change was in the same range of what is observed with GRE-EPI (~3–4 %), and the signal time course resembled the dynamics of what is typically observed with BOLD. Interestingly, no MRI contrast was observed with SWIFT between venous and arterial blood in vitro (Fig. 3) demonstrating that SWIFT, unlike GRE-EPI, is not sensitive to the shorter T₂ of the former. During respiratory challenges in the rat, the expected CBF increase was detected (Fig. 2, top panel) as a signal increase in the large vessels with SWIFT implemented with a local surface coil that renders the 3D acquisition inflow sensitive; conversely signal decreased in the cortex (Fig. 2, lower panel). Taken together, these findings suggest that blood oxygenation might significantly influence the SWIFT signal in vivo, through mechanisms which are not mediated by T₂ or T₂⁺ changes which dominate GRE-EPI BOLD fMRI. A possible explanation is that the SWIFT sequence, which is known to generate a chemical shift or frequency dependent phase during excitation/acquisition has an inherent intravoxel phase dispersion and hence signal cancellation in the presence of magnetic field inhomogeneities around blood vessels containing dHb; modulation of the dHb content then modulates this signal cancellation, thus providing a measure of the BOLD effect at zero TE. Alternatively or in addition, other cellular events associated with spins which are not visible at normal (finite) TE due to their ultrashort T₂ but detectable at TE=0 in SWIFT may contribute through T₁-changes, induced possibly by alterations in trans-membrane ion fluxes and coupled H₂O and/or H⁺ exchange between different tissue and cellular compartments. Regional tissue water content changes, such as changes in local blood volume, neuronal and/or glial swelling [4] and changes in arterial pressure [5] also have the potential to generate functional signals with SWIFT. However, such proton density changes might explain only signal changes < 1%. In conclusion, robust brain activation maps can be detected with SWIFT despite the absence of an echo. The development of fMRI protocols with SWIFT will likely have significant impact for brain mapping, thanks to the increased comfort for the subject, minimization of the acoustic noise, and less sensitivity to susceptibility artifacts typical of GRE-EPI techniques.

**References**


**Acknowledgments:** KECK Foundation, NIH Grants: BTRR-P41 RR008079, P30 NS057091, R01 NS061866, R21 NS059813, S10 RR023730, S10 RR027290.

**Figure 1.** Activation maps obtained with SWIFT (TR=5.2 s) during a visual stimulation paradigm from one representative subject, threshold p<3.3e⁻¹⁰

**Figure 2.** SWIFT signal time course (as a function of scan #, TR=3s) acquired on the rat brain at 9.4T. Shaded bars indicate when the ventilator was off.

**Figure 3.** 5-mm tube samples containing venous/arterial blood, imaged with SWIFT or GRE at 9.4T.
What is the ultimate sensitivity of fMRI: Does the whole brain activate?
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INTRODUCTION: Despite converging evidence suggesting that the whole brain is continuously working & adapting to anticipate & actuate in response to the environment, over the last 20 years fMRI have emphasized a localizationist view of brain function by showing only a handful of regions responding to task/stimulation. Here, we challenge that view with evidence that under optimal TSNR conditions, fMRI activations extent beyond areas of primary relationship to the task; and that task-correlated signal changes appear in over 90% of the brain for a visual stimulation + attention control task. Moreover, we show that responses vary greatly across regions; and that whole-brain parcellations based on response shape differences produce functionally meaningful clusters that are symmetrical across hemispheres; and reproducible across subjects and clustering algorithms. To do this, we acquired and combined 100 EPI scans (e.g., approx. 9 hours of data) in each of 3 subjects. This way we increased white matter TSNR by approx. a factor of 6 from TSNR_{raw}=339 to TSNR_{median}=2218.

METHODS: Task: Fig. 1 Data Acquisition: 100 functional scans (EPI, TR=2s, 32Slices, 3.8x3.8x3.8mm) were acquired in each of 3 subjects on a 3T scanner over the span of 10 visits. Data Pre-processing: physiological noise removal, slice timing correction; head motion correction, inter-run registration, discard first 5 volumes, remove fluctuations correlated with motion and its 1st derivative, intensity normalization. Statistical Analysis: to evaluate the effect of TSNR & versatility of response models on activation extent, statistical analysis with 3 different predictive response models (see Fig. 2) was conducted using only 5 runs (to simulate the amount of data on a regular study) or all 100 runs (to maximize TSNR). Percentage of significantly active voxels was computed for each case. Clustering: averaged trial responses (computed using all 500 trials) for each subject were input to both k-means (d=Pearson Correlation) and hierarchical clustering (link=ward; d=Euclidean) algorithms to evaluate if observed responses clustered spatially in a meaningful manner. We generated clusters for k levels ranging from 2 to 70.

RESULTS: The percent of active voxels increased markedly between 5 & 100 scans (Table 1) going from 16% (SUS Model; 5 Runs) to 95% (FIR Model; 100 Runs). Figure 2 shows the results of the k-means clustering for one representative subject and k=20. Figure 2.A shows a subset of responses associated with these clusters, which include: positive sustained (red & brown), negative sustained (light blue, green), and stimulus onset/offset responses (magenta and light brown). Within each of these 3 categories there are regional differences in magnitude, timing and actual shape. For example, responses C1 & C2 are both positively sustained; still C1 is smooth and has a descending ramp during the ON period. C2 is flat during the ON period and it has positive deflections at stimulus onset and offset. Differences in the post-stimulus undershoot also exists between C1 & C2. Similar arguments apply to the other responses. Figure 2.B shows the spatial distribution of clusters for K=20 (color coded in agreement with the time-series in 2.A). Clusters are not random, symmetrical across hemispheres and anatomically and functionally meaningful. For example, visual (red) and left motor cortices (brown) are part of different clusters (although both show positively sustained responses). Left (positively sustained, brown) and right (negatively sustained, blue) motor cortices are segregated into different clusters too. This agrees with the fact that subjects were responding using only their right hand. Left primary and supplementary motor cortices are part of the same cluster (brown). Finally, occipital cortex shows 3 different clusters in the anterior/posterior direction (red, magenta and green). Figure 4 shows clustering results for k=5 when the analysis is restricted to the subcortical grey matter (GM). Subcortical GM clusters agree to a great extent with anatomically based parcellations of these regions. When hierarchical clustering is attempted, results are very similar (not shown here) and the average cophenetic distance is 0.8.

DISCUSSION & CONCLUSIONS: The substantial increase in activation extent with number of scans and model versatility (Table 1) suggests that the sparseness of fMRI activation maps is not the result of truly isolated foci of activation, but a consequence of insufficient TSNR and overly strict predictive response models. Detected responses time-locked with task-timing go beyond those commonly used as markers of neuronal activity in fMRI i.e., positively sustained. Our results show that consideration of additional response shapes, and paying attention to subtle interregional differences in response shape, not only leads to increased volumes of activation, but has the potential to provide additional information about the functional organization of the brain in response to an external perturbation (task/stimulus). This is in agreement with previous studies [1,2,3]. Clustering permitted segregation of activated areas into groups of regions with similar response profiles. In other words, it permitted classification of voxels in a manner more informative than the common active/inactive dichotomy that results from the application of a given statistical threshold. Overall, these findings highlight the exquisite detail lying in fMRI signals beyond what it is normally tested for. They also emphasize the pervasiveness of false negatives in fMRI, and open interesting questions on how to analyze and interpret fMRI results in the near future when better hardware and software will allow attaining TSNR levels equivalent to the ones shown here with 100 scans using a practical number of scans.