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7T-fMRI: Faster temporal resolution yields optimal BOLD sensitivity for functional network imaging specifically at high spatial resolution

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Abstract

Recent developments in accelerated imaging methods allow faster acquisition of high spatial resolution images. This could improve the applications of functional magnetic resonance imaging at 7 Tesla (7T-fMRI), such as neurosurgical planning and Brain Computer Interfaces (BCIs). However, increasing the spatial and temporal resolution will both lead to signal-to-noise ratio (SNR) losses due to decreased signal intensity and T_1 -relaxation effect, respectively. This could potentially offset the SNR efficiency gains made with increasing temporal resolution.

We investigated the effects of varying spatial and temporal resolution on fMRI sensitivity measures and their implications on fMRI-based BCI simulations. We compared temporal signal-to-noise ratio (tSNR), normalized percent signal change (% ΔS), volumes of significant activation, Z-scores and decoding performance of linear classifiers commonly used in BCIs across a range of spatial and temporal resolution images acquired during an ankle-tapping task.

Our results revealed an average increase of 22% in % ΔS ($p=0.006$) and 9% in decoding performance ($p=0.015$) with temporal resolution only at the highest spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$, despite a 29% decrease in tSNR ($p<0.001$) and plateaued Z-scores. Further, the volume of significant activation was indifferent ($p>0.05$) across spatial resolution specifically at the highest temporal resolution of 500ms.

These results demonstrate that the overall BOLD sensitivity can be increased significantly with temporal resolution, granted an adequately high spatial resolution with minimal physiological noise level. This shows the feasibility of diffuse motor-network imaging at high spatial and temporal resolution with robust BOLD sensitivity with 7T-fMRI. Importantly, we show that this sensitivity improvement could be extended to an fMRI application such as BCIs.

Non-standard abbreviations - VV: Voxel Volume; % ΔS : observed percent signal change; tSD: temporal standard deviation; mROI: motor region of interest

Keywords: 7T, fMRI, sensitivity, temporal resolution; classification; BCI; physiological noise

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Non-standard abbreviations - VV: Voxel Volume; % ΔS : observed percent signal change; tSD: temporal standard deviation; mROI: motor region of interest

1 1. Introduction

2 *Functional magnetic resonance imaging at 7 Tesla (7T-fMRI) improves blood-*
3 *oxygenation level dependent (BOLD) signal specificity and sensitivity compared to lower*
4 *magnetic field strengths (De Martino et al., 2011; Duong et al., 2003; Gati et al., 1997;*
5 *Geissler et al., 2007; Okada et al., 2005; van der Zwaag et al., 2009; Vu et al., 2016a;*
6 *Yacoub et al., 2001a). These benefits are maximized at sufficiently high spatial resolutions*
7 *where the thermal noise dominates over the physiological noise (i.e., thermal noise*
8 *dominance) (Triantafyllou et al., 2005).*

9 *However, the number of serial slices needed to cover the desired field-of-view and the*
10 *number of independent phase encoding steps needed to achieve a given spatial resolution*
11 *(i.e., voxel volume; VV) limits the repetition time (TR) and thus temporal resolution in fMRI.*
12 *Recent developments in simultaneous multislice multiband (Moeller et al., 2010; Setsompop*
13 *et al., 2012) and parallel imaging techniques (Griswold et al., 2002; Pruessmann et al.,*
14 *1999; Sodickson and Manning, 1997) now allow for significantly shorter TRs without*
15 *compromising spatial resolution and coverage (Feinberg et al., 2010; Smith et al., 2013;*
16 *Ugurbil et al., 2013; Xu et al., 2013).*

17 *This potentially could improve SNR per unit time (i.e., SNR efficiency) and in turn*
18 *increase the statistical power (Constable and Spencer, 2001). However, increasing both*
19 *spatial and temporal resolution will also lead to SNR losses due to decreased net*
20 *magnetization per voxel and spin-lattice relaxation effect (i.e., T_1 -relaxation effect),*
21 *respectively. This could potentially offset the SNR efficiency gains made with increasing*
22 *temporal resolution. The SNR loss coupled with limitations in coverage may discourage*
23 *investigators from imaging at the desired combination of higher spatial and temporal*
24 *resolution.*

With this in mind, our primary aim was to investigate the relationship between TR and overall BOLD sensitivity. We compared the temporal SNR (tSNR), observed range of normalized percent signal change ($\% \Delta S$), volume of significant activation and Z-scores across images acquired at various spatial and temporal resolution during a cued ankle dorsiflexion task at 7T.

We hypothesized that the overall BOLD sensitivity would increase with temporal resolution despite a reduction in tSNR largely due to three factors. First, physiological noise level would decrease with increasing resolution. Physiological noise level scales proportionally to signal intensity and thus decreases with VV (Triantafyllou et al., 2005). Signal intensity also decreases with TR, as shorter TRs allow less time for the excited spins to return to thermal equilibrium (i.e., T_1 -relaxation effect). Hence, physiological noise level would also decrease with TR. Second, statistical power would increase with temporal resolution due to increased SNR efficiency (Constable and Spencer, 2001). Third, faster sampling at higher temporal resolutions would increase the observed BOLD contrast (i.e., $\% \Delta S$) due to less under-sampling, as well as the accuracy of statistical processing by better modelling of signal and nuisance covariates (Chang et al., 2013; Chen et al., 2015; Fera et al., 2004; Tong and Frederick, 2014). These factors are discussed in detail in Section 4.1 of Discussion.

Furthermore, the overall goal of our group is to use ultra-high field fMRI to investigate the feasibility of lower-limb motor-restorative Brain-Computer Interfaces (BCIs), as well as for training and surgical planning purposes. Previously, 7T-fMRI and electrocorticography (ECoG) have shown high spatial congruency (Siero et al., 2014) and fMRI has already been utilized for neurosurgical planning (Wengenroth et al., 2011; Zhang et al., 2015) and operating BCIs (Sousa et al., 2016; Weiskopf et al., 2004).

Therefore, our secondary aim was to investigate how the effects of spatial and temporal resolution on fMRI sensitivity would influence the performance of BCI simulations using 7T-fMRI. Faster temporal resolution has been shown to increase decoding performance by providing more BOLD information per unit time and more precise timing of experimental blocks (Chen et al., 2015; Vu et al., 2016b). We subjected the BOLD signal to a linear classifier commonly used in BCIs (Lotte et al., 2007) to decode various stages of the motor task. The hypothesis was that decoding performance will mirror the changes in BOLD sensitivity across imaging parameters, and hence increase with temporal resolution.

2. Materials and Methods

2.1. Participants

Ten neurologically normal right-footed volunteers (6 males and 4 females; mean $\pm$ standard deviation age: 25.4 ± 3.27 years) participated in a single-session fMRI experiment. Each participant gave informed consent prior to their participation. The data was anonymized before the analyses. The University of Melbourne Human Research Ethics Committee approved this study (Ethics ID: 1340926.1).

2.2. Image acquisition

All imaging was performed on a 7T research scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head-coil (Nova Medical Inc., Wilmington MA, USA). Structural images were acquired using Susceptibility Weighted Imaging (SWI; axial 3D-GRE, TE/TR/TA=15.3ms/20ms/8:42min, flip angle (FA)=13°, GRAPPA factor=3, Matrix=768x600x120, VV=0.3x0.3x1.2mm³, acquisition time = ~8mins).

All fMRI images were acquired using 2D gradient echo-echo planar imaging (GE-EPI) with multiband and parallel imaging acceleration (Siemens Healthcare prototype

research sequence). To demonstrate that physiological noise level scaled proportionally to signal intensity (Triantafyllou et al., 2005), five one-minute-long functional images were acquired with varying VVs (from $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to $3.5 \times 3.5 \times 3.5 \text{ mm}^3$ in increments of $0.5 \times 0.5 \times 0.5 \text{ mm}^3$) at a set TR of 500ms in the absence of a motor-task. These images will be commonly referred to as Non-task images.

To investigate the effects of imaging resolutions on overall BOLD sensitivity, fMRI images were acquired during the motor tasks using three different TRs (500ms, 1000ms and 2000ms), each at two different VVs ($1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and $2 \times 2 \times 2 \text{ mm}^3$). These images will be commonly referred to as Task images. The bandwidth ($\sim 1980 \text{ Hz/pixel}$), TE (30ms), in-plane field of view (FOV; $224 \times 224 \text{ mm}^2$), echo spacing (0.67ms), EPI factor (148), PE shift factor (2), Partial Fourier (6/8), acquisition direction (A-P), multiband factor (3), GRAPPA factor (3), number of slices (21; slice FOV = 31.5 mm for $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and 42 mm for $2 \times 2 \times 2 \text{ mm}^3$) and acquisition time (3.4min) were kept consistent across all GE-EPI scans to isolate the effects of imaging resolutions. Based on blood T_1 value of 2000ms at 7T (Hernandez-Garcia et al., 2007; Wright et al., 2008), the FA was set to the Ernst angle of 38° , 53° and 68° for TR of 500ms, 1000ms and 2000ms, respectively. Although minimum TE was 15ms at the highest resolution, 30ms was chosen based on previous studies where the physiological/thermal noise ratio (Triantafyllou et al., 2005; Figure 8b), t-value and $\% \Delta S$ peaked $\sim 30 \text{ ms}$ (Van Der Zwaag., 2009; Figure 3b & c, respectively).

Figure 1. A schematic of one experimental block of the ankle-tapping task. Each block consisted of 12s rest, 3s of prompt, then 5s of execution. The conditions left ankle and right ankle were repeated 4 times each in a pseudo-random order. Each task concluded with a final 15s of rest period.

2.3. fMRI experiment protocol

The participants engaged in six runs of a cued ankle-tapping task in two sets of three runs (i.e., one for each Task image). The VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ images were acquired first with increasing TR (500ms, 1000ms, then 2000ms). Then the VV of $2 \times 2 \times 2 \text{ mm}^3$ images were acquired with increasing TR also. This order was kept consistent across all participants except for the first two participants, whose images were acquired in the opposite order (see Discussion, Section 4.4). Non-task images were acquired in between the Task image sets. To minimize head movement during the tasks, participants' legs were slightly raised onto a support foam and strapped at the level of the mid-tibia. Participants followed the instructions on the screen during the motor tasks (Figure 1), which were also verbally explained prior to scanning. Otherwise they were asked to remain as still as possible.

2.3.1. Cued ankle dorsiflexion fMRI task

Before the task began, the words "Are you ready?" were presented for 30s. A trial consisted of a 12s rest block with a flashing fixation cross (white to red; 1Hz), followed by a 3s prompt block with a visual cue, either "LEFT ANKLE" or "RIGHT ANKLE", indicating which ankle was to be moved and lastly a 5s execution block with a visual cue, "GO", and a flashing prompt cue (white to red; 1Hz). The two conditions, left ankle (LA) and right ankle (RA), were repeated four times. The order of conditions was randomized for each imaging resolution. All experiments finished with 15s of rest block. The flashing rate of the stimulus in the execution blocks served as a guide of movement speed. The flashing of the fixation cross during rest blocks served to control for any potential activity evoked by this flashing during the execution blocks.

2.4. fMRI analysis

Four participants were excluded from Task image analyses because of severe motion artifacts in at least one of the functional runs. No participants were omitted for Non-task image analysis. The FMRIB's Software Library's (FSL v5.0.9) fMRI Expert Analysis Tool (FEAT v6.00) (Jenkinson et al., 2012) was used for all functional analyses.

All functional images were preprocessed with motion correction (MCFLIRT) (Jenkinson et al., 2002), high-pass filtering (0.01Hz) and brain extraction (BET2) (Jenkinson et al., 2005). No slice-timing corrections were employed given the fast TRs and the use of multiband acceleration.

Task images were spatially smoothed using a kernel size of 0mm (i.e., no smoothing) and 4mm (full-width-half-maximum), deriving two sets of pre-processed images per image. No spatial smoothing was applied to Non-task images. Retrospective physiological noise detrending was deliberately avoided to preserve the effects of imaging-resolution-dependent changes in physiological noise contribution.

2.4.1. Non-task image analysis

To demonstrate the putative characteristics of thermal and physiological noise in our own data set, we compared SNR and tSNR across various VVs (see Discussion 4.1.1 for the details on the characteristics of thermal and physiological noise). SNR was calculated specifically in a region of interest (ROI) within dorsomesial primary motor cortex (M1) by dividing the mean signal ($\bar{S}$) by noise. The ROIs were spherical and 12mm in diameter and were created manually for each spatial resolution. The locations of each ROI were visually examined. $\bar{S}$ was calculated by averaging the signal intensity of the voxels in the right dorsomesial M1 ROI across time. Noise was estimated by averaging the temporal standard deviation (tSD) of voxels in a non-biological ROI (i.e., top left corner of the central slices

with no biological tissue). Hence, the noise was assumed to be largely from non-physiological sources (i.e., thermal noise), albeit not exclusively due to g-factor penalty implied by slice aliasing. With this assumption, SNR was expected to increase linearly with VV (Edelstein et al., 1986; Triantafyllou et al., 2005).

$tSNR$ was calculated for each Non-task image by dividing $\bar{S}$ by the noise. Both $\bar{S}$ and noise were calculated from the voxels encompassing the right dorsomesial M1 ROI for each participant. Hence, the noise was assumed to be of both non-physiological and physiological sources. With this assumption, $tSNR$ was expected to increase with VV but reach an asymptotic limit of $1/\lambda$ where:

$$tSNR = \frac{k \times VV}{\sqrt{1 + \lambda^2 + k^2 + VV^2}}, \quad (\text{Triantafyllou et al., 2005}).$$

This Triantafyllou model posits that SNR is a product of VV and proportionality constant k , and λ is a constant proportional to physiological components of noise, and thus is dependent on TE and change in $1/T_2^*$ (i.e., ΔR_2^* ; $\lambda = \sqrt{c_1^2 \times \Delta R_2^{*2} \times TE^2 + c_2^2}$; $c = \text{constant}$ proportional to signal intensity). Our $tSNR$ values were fitted with the Triantafyllou model to demonstrate that physiological noise scales proportionally to signal intensity.

2.4.2. Task image analysis

Statistical analyses were performed at the individual level using FMRIB's Improved Linear Model (FILM) (Woolrich et al., 2001). The left ankle and right ankle execution blocks (LA and RA, respectively) were modelled with a 5s-boxcar function convolved with a gamma function with a mean delay of 6s ($SD=3s$). Time points of large motion outliers were added as nuisance variables for all models. Congruent high-pass temporal filtering applied to the data was also applied to the models. Temporal derivatives of the models were added to cater for the potential temporal discrepancies between the data and model (Woolrich et al., 2001).

Z-score maps for LA and RA were contrasted against baseline (LA>rest and RA>rest) and each other (LA>RA, and RA>LA). Significant activation was defined using a lower Z-score threshold of 2.3 ($p < 0.01$, cluster-based correction; more stringent than the default setting of $p < 0.05$).

These significant activation maps were masked with a participant and imaging parameter specific motor region of interest (mROI) mask to ensure fair comparisons of fMRI sensitivity measures across participants and imaging parameters. The mROI masks encompassing both the supplementary motor area (SMA) and M1 were created using FSL and Advanced Normalisation Tools (ANTs) (Avants et al., 2011) in the following steps.

Probability maps of M1 and SMA in MNI space were each derived from Harvard-Oxford Cortical Atlas (Desikan et al., 2006) using built-in FSL functions. These maps were thresholded with a lower-limit of 25% to reduce the masks spilling into the neighbouring cortical regions. The resulting images were merged then binarized to create an mROI mask encompassing SMA and M1 in MNI space. MNI_152_1mm brain image was non-linearly registered to participant's SWI magnitude image space using ANTs. Participants' SWI images were linearly registered to each of their Task images. Using the warp and affine registration information acquired from the above steps, the mROI mask in MNI space were registered non-linearly to the SWI magnitude space, then linearly to each of the EPI spaces at the individual level using ANTs. In turn, six mROI masks were created for each participant (3 different TRs at 2 different VVs).

All fMRI sensitivity measures were calculated from significant voxels of all four contrasts within this mROI (i.e., SMA plus M1). tSNR was calculated by dividing the $\bar{S}$ by the noise. $\bar{S}$ was calculated by averaging the signal intensity across time for each voxel. Noise was calculated by averaging the tSD of the residuals after fitting the linear model from the

same set of voxels. These $tSNR$ values were averaged across voxels and contrasts then compared across imaging resolutions.

To calculate $\% \Delta S$, the BOLD signal time-course from the preprocessed data was normalized by dividing the signal intensity by the temporal mean at the voxel level. This normalized BOLD time-course was averaged across voxels within the mROI. The range in this averaged normalized signal was calculated by subtracting the minimum value from the peak value within each trial. Finally, these values were averaged across trials and contrasts.

Volume of significant activation was calculated by averaging the volume of all significant voxels across all contrasts within the mROI using FSL's built-in commands. Z-scores were calculated by averaging the Z-scores of voxels across all contrasts using FSL's built-in commands.

Repeated measures analysis of variance (rmANOVA) was used to investigate significant changes in the sensitivity measures across TR and VV, after testing for the violation of assumptions and correcting for the violations when appropriate (Greenhouse-Geisser correction). Pairwise comparisons testing with Bonferroni correction were carried out when overall significant changes were observed.

2.5. Time-resolved fMRI analysis

To generate appropriate data for investigating the potential implications of varying imaging resolutions on simulating BCIs via fMRI, a time-resolved fMRI analysis was conducted at the individual level using the preprocessed Task images without smoothing. Putatively, the onset of SMA activation precedes that of M1 during voluntary movements given its involvement in higher order motor cognitions (Cunnington et al., 2003; Cunnington et al., 2006; Deecke et al., 1969). Not catering for these spatiotemporal differences of activation patterns could thus spatially bias the results. Hence, to delineate the voxels in

regions corresponding to higher order cognition from motor execution command, the prompt and execution blocks were modelled separately. Further, in an attempt to preserve the close temporal differences between the regressors, the boxcar functions were not convoluted but delayed by 4s to cater for the hemodynamic response delay. This technique was adopted from a previous work investigating this exact phenomenon (Cunnington et al., 2006).

The Z-score maps for the prompt blocks were contrasted against baseline not against each other (i.e., prompt>rest), as SMA putatively activates bilaterally prior to motor execution (Cunnington et al., 2003; Cunnington et al., 2006; Deecke et al., 1969). The Z-score maps of LA and RA (i.e., execution blocks) were contrasted against each other (i.e., LA>RA and RA>LA), as contralateral activation is putative for M1 during voluntary unilateral limb movements and to also eliminate any regions activating in both conditions (e.g., higher order motor cognition in the SMA). Significant activation was defined using a lower Z-score threshold of 2.3 (with $p<0.01$ for significance testing; cluster-based correction).

Note that unlike the study by Cunnington et al. (2006), there was no delay between prompt and execution blocks in the current experiment. This could have led to overlapping of BOLD activity corresponding to prompt and execution blocks in some voxels which may not have been modelled by the time-resolved approach. However, this study was not directly concerned with these regions of overlap as mentioned above. The high spatial resolution, high temporal resolution, lack of spatial smoothing and the contrasting of the two execution periods against each other reduced the likelihood of these voxels reaching significance.

2.5.1. Spatiotemporal classification of task-driven BOLD signal fluctuation

To investigate the potential implications of varying imaging resolutions on fMRI-based BCIs, the percentage of correct classifications of experimental blocks by a linear

classifier (decoding performance) was compared across imaging parameters. The normalized signal time-course from significant voxels within SMA and M1 were separately subjected to linear discriminant analysis commonly used in BCIs (Lotte et al., 2007).

Participant and imaging parameter specific masks were created separately for SMA and M1 using the exact same procedure described in Section 2.4.2, except the probability maps of SMA and M1 in MNI space were never merged. Voxels showing significant activation during prompt>rest were masked with the SMA mask. Voxels showing significant activation during LA>RA or RA>LA were masked with the M1 mask. Then, the normalized signal time-series of each voxel were extracted using FSL's `fslmeans` function.

For each contrast, the normalized signal time-course from all significant voxels within the mROIs were included for linear classification using linear discriminant analysis via custom script written in MATLAB (MathWorks Inc., Natick MA, version R2015b). Data was trained and decoded using all time points with a 4s-shifting-window against a stationary 4s window in the middle of the rest period (i.e., 14s – 18s after start of prompt blocks). At each time-point, the classifier was trained with the data points from all but one trial, within a 4s window defined as “1” (i.e., active) and the stationary 4s window in rest period as “0” (i.e., baseline). The classifier then decoded whether the data from the remaining trial was either “1” or “0”. This was validated by a leave-one-out cross validation method, whereby each comparison was permuted by the number of trials of a given block, with no repeats. This process was repeated as the window shifted across time.

The decoding performance was averaged across voxels, trials and the time points of expected BOLD activation respective to the voxel's cortical location. For voxels within SMA (i.e., prompt>rest contrast), this period was defined as 4s after the start of prompt block and 4s after the end of the execution blocks. For voxels within M1, it was defined as 4s after the

start and end of the execution blocks. The resulting values were then averaged across contrasts and compared between the imaging parameters.

3. Results

3.1. Significant BOLD activation was observed in the mROI during the motor task

Significant BOLD activation was observed for all contrasts ($Z > 2.3$, $p < 0.01$; cluster-wise corrected) in all participants for every combination of analytic and imaging resolutions, except for the contrast of LA>RA at $VV = 2 \times 2 \times 2 \text{ mm}^3$ and $TR = 1000 \text{ ms}$ with 4mm spatial smoothing for participant 3. Visual inspection at the individual level confirmed that significant activation was observed in the bilateral dorsomesial M1 and bilateral SMA for LA>rest and RA>rest. Significant activation was observed almost exclusively in the contralateral dorsomesial M1 in a highly localized fashion when the movement conditions were contrasted over each other. Figure 2 shows regions where significant voxels for LA>RA and RA>LA across individuals intersected with each other in MNI space. The locations of the clusters' centers of gravity can be found in Appendix A.

Figure 2. Locations where significant activations for the contrasts LA>RA (red) and RA>LA (blue) analysed at the individual level intersected across all participants in MNI space. Left ankle and right ankle execution specific activation was observed in the contralateral M1 in a highly lateralized manner across all parameters.

3.2. *fMRI sensitivity measures from Non-task images: SNR increased linearly while tSNR plateaued with voxel volume*

Figure 3 plots participant average SNR and tSNR as a function of VV. Overall, SNR increased linearly with VV ($F_{(2.3,20.7)}=44.21$, $p<0.001$; Greenhouse-Geisser corrected; goodness of fit to a linear model $R^2=0.93$). Pairwise comparisons testing revealed a significant increase in SNR from VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to $2 \times 2 \times 2 \text{ mm}^3$ ($p=0.003$), $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ ($p=0.002$), $3 \times 3 \times 3 \text{ mm}^3$ ($p=0.004$), and $3.5 \times 3.5 \times 3.5 \text{ mm}^3$ ($p<0.001$). SNR also increased to VV of $3.5 \times 3.5 \times 3.5 \text{ mm}^3$ from $2 \times 2 \times 2 \text{ mm}^3$ ($p<0.001$), $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ ($p=0.001$) and $3 \times 3 \times 3 \text{ mm}^3$ ($p=0.005$).

Overall, tSNR increased asymptotically with VV ($F_{(2.5,22.5)}=68.49$, $p<0.001$; Greenhouse-Geisser corrected; goodness of fit to Triantafyllou model, $R^2=0.97$; $\lambda=0.0124$ with lower and upper 95% confidence limits equal to 0.0097 and 0.0151, respectively; Figure 3b). Pairwise comparisons testing revealed that tSNR increased significantly from VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to all larger VVs (all $p<0.001$); from $2 \times 2 \times 2 \text{ mm}^3$ to $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ ($p=0.002$) and all larger voxels ($p<0.001$); and from $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ to $3 \times 3 \times 3 \text{ mm}^3$ ($p=0.042$) and $3.5 \times 3.5 \times 3.5 \text{ mm}^3$ ($p=0.001$).

3.3. *fMRI sensitivity measures calculated from Task images: Overall fMRI sensitivity increased with temporal resolution only at the higher spatial resolution*

Table 1 depicts the various fMRI sensitivity measures averaged across voxels, contrasts and participants.

3.3.1. *tSNR decreased with temporal resolution at spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$*

As shown in Figure 3c, tSNR decreased significantly with TR with no spatial smoothing at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ($F_{(1.1,5.3)}=33.46$, $p=0.002$; Greenhouse-Geisser

corrected). $tSNR$ decreased to 16.26 ± 0.79 at TR of 500ms from 1000ms (22.83 ± 0.88 ; $p < 0.001$) and 2000ms (29.45 ± 2.34 ; $p = 0.003$). $tSNR$ also decreased with TR when using a 4mm smoothing kernel ($F_{(2,10)} = 15.65$, $p = 0.001$). $tSNR$ decreased to 86.41 ± 3.58 at TR of 1000ms from 2000ms (107.76 ± 6.05 ; $p = 0.004$).

3.3.2. $tSNR$ decreased with temporal resolution at spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$

As shown in Figure 3c, $tSNR$ decreased significantly with TR with no spatial smoothing at VV of $2 \times 2 \times 2 \text{ mm}^3$ ($F_{(2,10)} = 26.27$, $p < 0.001$). $tSNR$ decreased to 26.13 ± 1.74 at TR of 500ms from 1000ms (34.80 ± 1.95 ; $p = 0.001$) and 2000ms (44.14 ± 4.53 ; $p = 0.005$). $tSNR$ also decreased with TR with 4mm smoothing ($F_{(2,10)} = 22.55$, $p < 0.001$; Figure 3c). $tSNR$ decreased to 76.21 ± 5.21 at TR of 500ms from 1000ms (93.95 ± 6.15 ; $p = 0.002$) and 2000ms (109.24 ± 10.83 ; $p = 0.009$).

3.3.3. $tSNR$ decreased with spatial resolution at all temporal resolutions, only without spatial smoothing

As shown in Figure 3c (top), the $tSNR$ decreased significantly from VV of $2 \times 2 \times 2 \text{ mm}^3$ to $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ across all TRs only with no spatial smoothing (500ms: $p = 0.001$; 1000ms: $p < 0.001$; and 2000ms: $p = 0.002$). $tSNR$ did not change across VV when 4mm smoothing kernel was used.

3.3.4. $\% \Delta S$ increased with temporal resolution only at the higher spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$

As shown in Figure 3d, $\% \Delta S$ increased significantly with temporal resolution with no spatial smoothing at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ($F_{(2,10)} = 20.62$, $p < 0.001$). $\% \Delta S$ increased to $7.90 \pm 0.56\%$ at TR of 500ms from 1000ms ($6.13 \pm 0.11\%$; $p = 0.006$). There were no other

329 significant differences in % ΔS between the TRs ($p>0.050$). % ΔS also increased with temporal
 330 resolution with 4mm smoothing ($F_{(2,10)}=7.72$, $p=0.009$). % ΔS increased to $3.22\pm0.21\%$ at TR
 331 500ms from 2000ms ($2.53\pm0.09\%$; $p=0.016$). The % ΔS did not differ across TR at VV of
 332 $2\times2\times2\text{mm}^3$ ($p>0.050$).
 333

Table 1. t SNR, % ΔS , volume of activation and Z-scores averaged across voxels, contrasts and participants

t SNR (SE)		TR(ms)		
VV(mm ³)	Smoothing	500	1000	2000
1.5x1.5x1.5	0mm	16.26 (0.79)	22.83 (0.88)	29.45 (2.34)
	4mm	82.46 (3.45)	86.41 (3.58)	107.76 (6.05)
2x2x2	0mm	26.13 (1.74)	34.80 (1.95)	44.14 (4.53)
	4mm	76.21 (5.21)	93.95 (6.15)	109.24 (10.83)
% ΔS (SE)		TR(ms)		
VV(mm ³)	Smoothing	500	1000	2000
1.5x1.5x1.5	0mm	7.90 (0.56)	6.13 (0.11)	6.76 (0.21)
	4mm	3.22 (0.21)	2.79 (0.10)	2.53 (0.09)
2x2x2	0mm	5.63 (0.46)	5.61 (0.38)	5.36 (0.25)
	4mm	3.01 (0.23)	2.96 (0.21)	2.82 (0.12)
Volume(mm ³) (SE)		TR(ms)		
VV(mm ³)	Smoothing	500	1000	2000
1.5x1.5x1.5	0mm	2845.37 (179.01)	1987.92 (346.86)	2069.53 (255.20)
	4mm	9363.76 (554.69)	6165.48 (1283.90)	7137.18 (905.84)
2x2x2	0mm	4146.00 (752.86)	5435.67 (589.80)	5126.67 (1031.19)
	4mm	8870.67 (1680.06)	11471.00 (1673.33)	10674.33 (1967.61)
Z-score (SE)		TR(ms)		
VV(mm ³)	Smoothing	500	1000	2000
1.5x1.5x1.5	0mm	3.63 (0.07)	3.80 (0.12)	3.15 (0.07)
	4mm	4.19 (0.12)	4.46 (0.10)	3.25 (0.23)
2x2x2	0mm	3.54 (0.10)	3.28 (0.04)	3.61 (0.16)
	4mm	3.89 (0.15)	3.51 (0.03)	4.01 (0.21)

SE=standard error; TR=repetition time

3.3.5. Volume of significant activation was indifferent across the spatial resolutions only at the higher temporal resolution

As shown in Figure 3e, the volume of significant activation did not differ across VV at TR of 500ms, or across TR at either VV ($p>0.050$). However, the volume of significant activation did increase significantly from VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to $2 \times 2 \times 2 \text{ mm}^3$ at TR of 1000ms and 2000ms with no spatial smoothing (1000ms: $F_{(1,5)}=23.24$, $p=0.005$; 2000ms: $F_{(1,5)}=11.82$, $p=0.018$) and with 4mm smoothing (1000ms: $F_{(1,5)}=9.23$, $p=0.029$; 2000ms: $F_{(1,5)}=7.15$, $p=0.044$).

3.3.6. Z-scores increased significantly with temporal resolution up to 1000ms at spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$

As shown in Figure 3f, Z-scores changed significantly with temporal resolution with no spatial smoothing at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ($F_{(2,10)}=17.30$, $p=0.001$). Z-scores increased from TR of 2000ms (3.15 ± 0.12) to 1000ms (3.80 ± 0.12 ; $p=0.017$) and 500ms (3.63 ± 0.7 ; $p=0.006$). Z-scores did not differ between TR of 500ms and 1000ms. Z-scores also changed significantly with temporal resolution with 4mm spatial smoothing ($F_{(1,1,5,5)}=15.60$, $p=0.008$). Z-scores increased from TR of 2000ms (3.25 ± 0.23) to 1000ms (4.46 ± 0.10 ; $p=0.036$) and 500ms (4.19 ± 0.12 ; $p=0.005$). Z-scores did not differ between TR of 500ms and 1000ms.

3.3.7. Z-score increased significantly with temporal resolution up to 500ms at the spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$

As shown in Figure 3f, Z-scores changed significantly with temporal resolution with no spatial smoothing at VV of $2 \times 2 \times 2 \text{ mm}^3$ ($F_{(2,10)}=4.79$, $p=0.035$). Z-scores increased from TR of 1000ms (3.27 ± 0.036) to 500ms (3.54 ± 0.10 ; $p=0.006$). Z-scores did not differ between any other TRs or with 4mm smoothing.

Figure 3. (a) The participant average SNR and (b) tSNR across varying voxel volume (VV) with a set repetition time (TR) of 500ms within the mROI of Non-task Images. The SNR increased linearly, while tSNR increased asymptotically with VV. (c) tSNR; (d) observed range of normalized percent signal change (%ΔS); (e) volume of significant activation within the mROI; and (f) Z-scores averaged across all significant voxels and participants as a function of TR, at VV of 1.5x1.5x1.5mm³ (blue) and 2x2x2mm³ (red) and two separate smoothing levels, (top row) 0mm, and (bottom row) 4mm. All error bars indicate standard error across participants. tSNR decreased with TR with or without smoothing, while there was a significant increase in %ΔS with decreasing TR only at 1.5x1.5x1.5mm³. Z-scores increased from TR of 2000ms to 1000ms at VV of 1.5x1.5x1.5mm³ and from 1000ms to 500ms at VV of 2x2x2mm³. The volume of significant activation did not differ across TR at all, or across VV at TR of 500ms.

3.4. Time-resolved fMRI analysis: Spatiotemporal dynamics of BOLD signal changes were more evident at higher temporal resolution only at the higher spatial resolution

For all participants, significant activations were observed in the contralateral dorsomesial M1 for the contrasts LA>RA and RA>LA at both TRs and VVs. Significant activations during the prompt blocks were observed in SMA bilaterally at all TRs and VVs, except for participant 3 at VV of $2 \times 2 \times 2 \text{ mm}^3$ and TR of 500ms. Hence, subsequent analyses involving the prompt blocks at VV of $2 \times 2 \times 2 \text{ mm}^3$ and TR of 500ms included data from only five participants. All six participants were included for all other analyses. Figure 4c shows the regions of activations for a representative participant (participant 4; See Appendix E for the rest).

As shown in Figure 4a, Wilcoxon rank sum tests revealed a significant increase in average $\% \Delta S$ across contrasts to 500ms (mean $\pm$ SE; $8.47 \pm 0.35\%$;) from 2000ms ($6.15 \pm 0.54\%$) only at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ($p=0.026$). There was no significant difference in $\% \Delta S$ between the TRs at VV of $2 \times 2 \times 2 \text{ mm}^3$. Table 2 displays the participant average of $\% \Delta S$ values during the prompt blocks, execution blocks and the average across both conditions. Note for Figure 4a, the x-axes start at 4s as it is aligned to the decoding windows for ease of interpretation (i.e., 4s of data was used for each decoding time point).

3.4.1. The decoding performance of linear classifiers was more accurate at the higher temporal resolution only at the higher spatial resolution

Wilcoxon rank sum tests revealed a significant increase in average decoding performance during active blocks across all contrasts from TR of 2000ms ($90.52 \pm 2.43\%$) to 500ms ($98.71 \pm 0.62\%$; $p=0.026$) and 1000ms ($98.88 \pm 0.54\%$; $p=0.015$) only at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$. The decoding performance did not differ across TR at VV of $2 \times 2 \times 2 \text{ mm}^3$. Table 3 depicts the participant average of decoding performance across the active periods

385 *for prompt and execution, and the average of both conditions. Figure 4b plots the participant*
386 *average of decoding performance at each time-point for all imaging parameters.*

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387 Table 2. Region and contrast specific observed range of normalized signal changes (% ΔS) averaged across voxels, trials and participants

Region ^a	Trial mean % ΔS averaged across participants (standard error) %					
	Voxel Volume					
	1.5x1.5x1.5mm ³			2x2x2mm ³		
	TR=500ms	TR=1000ms	TR=2000ms	TR=500ms	TR=1000ms	TR=2000ms
SMA(prompt)	6.78 (0.60)%	5.98 (0.58)%	5.11 (0.69)%	5.11 (0.86)%	4.36 (0.41)%	3.45 (0.41)%
M1(LA)	8.49 (0.45)%	7.34 (0.41)%	6.75 (0.86)%	6.64 (0.89)%	5.68 (0.39)%	4.91 (0.48)%
M1(RA)	10.15 (1.08)%	7.98 (1.18)%	6.60 (0.69)%	6.96 (1.16)%	6.02 (0.58)%	5.67 (1.02)%
M1+SMA ^b	8.47 (0.35)%	7.10 (0.61)%	6.15 (0.54)%	6.44 (0.75)%	5.35 (0.37)%	4.68 (0.49)%

^aRegions of significant activation for the specified contrasts; ^bAverage values across all contrasts

388 Table 3. Region and contrast specific average decoding performances during active periods averaged across voxels, trials and participants

Region ^a	Maximum trial mean percentage of correct classification averaged across participants (standard error) %					
	Voxel Volume					
	1.5x1.5x1.5mm ³			2x2x2mm ³		
	TR=500ms	TR=1000ms	TR=2000ms	TR=500ms	TR=1000ms	TR=2000ms
SMA(prompt)	98.22 (0.72)%	99.07 (0.48)%	81.46 (5.43)%	96.47 (2.25)%	93.63 (5.19)%	83.75 (7.60)%
M1(LA)	99.05 (0.68)%	98.61 (0.63)%	93.75 (3.21)%	95.45 (3.95)%	95.49 (3.75)%	97.92 (1.41)%
M1(RA)	98.86 (0.71)%	98.96 (0.95)%	96.35 (2.26)%	96.78 (1.70)%	96.18 (2.75)%	94.27 (3.25)%
M1+SMA ^b	98.71 (0.62)%	98.88 (0.54)%	90.52 (2.43)%	95.45 (2.48)%	95.10 (3.88)%	91.98 (3.40)%

^aRegions of significant activation for the specified contrasts; ^bAverage values across all contrasts

Figure 4. (a) Time-courses of normalized percent signal change and (b) average decoding performances averaged across voxels, trials and participants at various time points from voxels showing significant activations during prompt and execution blocks in bilateral SMA and contralateral M1, respectively. The vertical blue lines denote the start of the prompt block, and the vertical red lines denote the start of movement execution block, both with a temporal delay of 4s. The shading denotes the standard error across participants. (c) Regions of significant activation for the contrasts of LA>RA (red) and RA>LA (green) in M1, and prompt>rest (blue) in SMA for in slices 5, 9, 13 and 17 for participant 4 overlaid onto the multiband functional images. Each background EPI image was scaled arbitrarily to produce similar contrast across different imaging parameters (unscaled images can be seen in Appendix F). The yellow box illustrates the approximate coverage achieved with all 21 slices, with the raw functional image in blue. Average range of normalized percent signal change and decoding performance across all contrasts increased significantly with temporal resolution, only at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$.

4. Discussion

The current results indicate that BOLD sensitivity can be increased with temporal resolution, however it is dependent on the spatial resolution. Only at the highest spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$, $\% \Delta S$ and decoding performance increased while Z-scores plateaued. Further, the volume of significant activation was indifferent ($p > 0.05$) across the spatial resolutions exclusively at the shortest TR of 500ms despite a significant decrease in tSNR (Figure 3). These findings suggest that for functional imaging of neural networks at 7T, increasing the temporal resolution could not only compensate but also exceed the effect of subsequent decrease in tSNR, given an adequately high spatial resolution¹ with minimal physiological noise level.

Based on our findings, we suggest increasing the temporal resolution to maximize the BOLD sensitivity for high spatial resolution imaging of a neural network at 7T (i.e., $VV \leq 1.5 \times 1.5 \times 1.5 \text{ mm}^3$; slice FOV $\approx 31.5 \text{ mm}$). However, at lower spatial resolutions with higher tSNR and physiological noise level, faster temporal resolutions may not significantly improve the overall BOLD sensitivity and not be worth the limitations in coverage. Although, faster temporal resolution did increase the statistical power at the lower resolution and could also improve other aspects of post-processing that were not tested directly in this study (i.e., retrospective physiological noise removal). These findings highlight the importance of optimizing imaging parameters specifically for the purpose of a given study.

4.1. Faster temporal resolution increases overall BOLD sensitivity at 7T, specifically at high spatial resolution imaging of a functional network

The current interaction effect of spatial and temporal resolution on BOLD sensitivity was attributed to the following factors.

¹ Please note that “high spatial resolution” in this instance considers the inherent limitations in VV implied by the necessary coverage to encompass a functional network.

4.1.1. Factor 1: Physiological noise level decreased with increasing temporal and spatial resolution

It was determined that physiological noise level decreased with increasing spatial and temporal resolution for the following reasons. Physiological noise is a temporally and spatially correlated source of noise that scales proportionally to MR signal intensity. Given that smaller VV entails less net magnetization per voxel and thus signal intensity, physiological noise level decreases linearly with VV (Biswal et al., 1995; Dagli et al., 1999; Kruger and Glover, 2001; Triantafyllou et al., 2005; Weisskoff et al., 1993). In contrast, thermal noise is Gaussian in nature and its amplitude is primarily determined by the coil-loading and is independent of VV (Triantafyllou et al., 2005).

Signal intensity also decreases with TR due to the T_1 -relaxation effect, where the excited spins are not permitted enough time to relax back to thermal equilibrium before the subsequent excitation radio-frequency pulse. Using excitation flip angles at the Ernst angle for a given TR reduces this effect. However, signal intensity still decreases with TR as smaller flip angles entail less net transverse magnetization (Appendix F). Thus, physiological noise would also decrease with TR.

Although it would have been ideal to acquire “flip angle of 0° ” images that are needed for measuring thermal noise level and calculating the physiological noise level in isolation, they could not be acquired due to technical difficulties. These characteristics of physiological and thermal noise are often just assumed, however, we have demonstrated them in the current dataset for completeness.

Considering the characteristics described above, tSNR was expected to increase with VV with an asymptotic limit of $1/\lambda$, as implied by the Triantafyllou model, while SNR increased linearly with VV (Triantafyllou et al., 2005). λ is a constant proportional to

physiological components of noise (see Section 2.4.1 in Methods for the equation). This is because the only factor that differed across calculating these measures was where the noise was estimated from. For $tSNR$, noise was measured from the same voxels where the mean signal was calculated from. Hence, the noise was assumed to be made up of both non-physiological (i.e., thermal noise) and physiological sources. For SNR , it was measured from a non-biological ROI away from the head. Hence, the noise was assumed to be made up of thermal noise, albeit not exclusively. The use of high acceleration factors and the partial coverage would have increased slice-leakage and g-factor penalty (Moeller et al., 2010; Setsompop et al., 2012) and may have caused aliasing of physiological noise from biological voxels into the non-biological ROI. This factor may have been greater in the higher spatial resolution images given the smaller slice FOV with reduced coil sensitivity.

Despite the issue of slice-leakage and g-factor penalty, our results revealed a linear increase in SNR with VV while $tSNR$ increased asymptotically with VV. The Triantafyllou model fitted well with our $tSNR$ values, where our λ value of 0.0124 was strikingly similar to the one calculated by the original authors at 7T using a GE-EPI sequence ($\lambda=0.0113$ with lower and upper 95% confidence limits equal to 0.0102 and 0.0123). This validated our assumption that physiological noise level decreased with both VV and TR.

This assumption was extended to the task fMRI data as $tSNR$ values at corresponding imaging resolutions across the Task and Non-task images were virtually identical. Furthermore, the significant differences in the Task image $tSNRs$ across VV were no longer observed when the images were spatially smoothed (Figure 3). Spatial smoothing renders the noise distribution more Gaussian while preserving task-driven signal changes by averaging the signal intensity across neighbouring voxels, in turn increasing SNR and $tSNR$ (Worsley et al., 2002). Hence, in the current study, the images with less physiological noise contribution

(i.e., higher spatial resolution images) would have benefited more from spatial smoothing (Triantafyllou et al., 2006).

This study adds to the previous work on characteristics of physiological noise in relation to signal intensity at 7T by: (1) using a 2D GE-EPI sequence with high acceleration factors using both multiband and parallel techniques; (2) using a 32-channel head-coil; (3) using both task and non-task fMRI; and (4) demonstrating the isolated effects of spatial and temporal resolution by keeping all other imaging parameters consistent. With empirical evidence of thermal noise dominance at VV of $1 \times 1 \times 1 \text{ mm}^3$ and TR of 5400ms at 7T (Triantafyllou et al., 2005; Triantafyllou et al., 2016), the current highest resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and 500ms was assumed to have thermal noise dominance with minimal physiological noise contribution.

4.1.2. Factor 2: Statistical power increased with temporal resolution

Our results indicate that the statistical power increased with temporal resolution due to the increase in the number of images acquired per slice (i.e., SNR efficiency), given the fixed experiment duration in this study (Constable and Spencer, 2001). This is reflected by the increase in Z-scores with temporal resolution at both spatial resolutions. At VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ Z-scores increased from 2000ms to 1000ms then plateaued, which is consistent with previous work by Constable and Spencer (2001). At VV of $2 \times 2 \times 2 \text{ mm}^3$ Z-scores increased from TR of 1000ms to 500ms only. Hence, some sensitivity could indeed be recovered with faster temporal resolution, even at the lower resolution. However, as we show, temporal resolution dependent increase in $\% \Delta S$ was not observed at the lower spatial resolution. Thus, whether the increase in statistical power alone is worth the limitations in coverage and tSNR loss would depend on the purpose of a given study. This non-linear interaction effect of spatial and temporal resolution on statistical power was determined to

be driven by physiological noise level differences across the different spatial resolutions (see Section 4.1.4).

4.1.3. Factor 3: Observed BOLD contrast increased with temporal resolution

As we hypothesized, the observed BOLD contrast (i.e., $\% \Delta S$) increased with temporal resolution, presumably due to faster sampling of signal less plagued by physiological noise. A faster temporal resolution entails less under-sampling of signal, which could have increased the observed range of signal (Figure 4a). We validated this effect by downsampling the TR of 500ms data at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to 1000ms and 2000ms by subsampling every second and fourth data points, respectively (Appendix D). As expected, $\% \Delta S$ increased significantly with temporal resolution (Wilcoxon rank sum test; all $p < 0.01$). It should be noted that the irreversible effects of longer TRs (e.g., increased physiological noise contribution, loss in temporal information, increased T_1 -weighting) would not be inherent in the downsampled data. This would have only underestimated the current effect during the simulation.

In addition, a faster temporal resolution could have further increased the apparent BOLD contrast by improving the accuracy of statistical modelling and nuisance covariates (Chang et al., 2013; Chen et al., 2015; Fera et al., 2004; Tong and Frederick, 2014). This would increase the likelihood of identifying the voxels that truly correspond to the task at hand, which should in theory have greater $\% \Delta S$ than noisy voxels. Consistently, in the absence of retrospective physiological noise detrending, the highest combination of spatial and temporal resolution with the least physiological noise contribution revealed the largest $\% \Delta S$.

We do note that the average $\% \Delta S$ values in Figure 3c seemed to have increased from TR of 1000ms to 2000ms at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$. Although this difference was insignificant

($p > 0.05$), this trend could indeed seem unusual. We attribute this insignificant effect to the lack of spatial separation within the mROI. SMA and MI have characteristically different BOLD activation profiles as observed in the time-resolved fMRI analysis (Figure 4a) and as discussed in Section 4.2 below. It is likely that SMA voxels corresponding to the higher-order motor cognition may have been identified as activating in Task image analysis, given the close temporal proximity of prompt and execution blocks, lack of prompt block modelling and inclusion of temporal derivative functions in GLMs. The extent of this effect should have been greater at the longer TRs which could account for this unusual trend. Consistently, the trend was no longer observed in the time-resolved fMRI analysis where SMA and MI were separated (Figure 4a) or in the simulated data with identical voxel location (Appendix D).

4.1.4. Factor 4: Differing levels of physiological noise across spatial resolutions modulated the previous factors

Lastly, the varying levels of physiological noise level across different spatial resolutions seemed to have influenced the factors mentioned above, in turn creating an interaction effect between the two resolution realms. As we have extensively discussed in Section 4.1.1, it was assumed that physiological noise was higher at the lower spatial resolution. This can readily explain why the trend of current effect, namely, temporal resolution dependent changes in BOLD sensitivity measures, differed across spatial resolutions.

For example, the Z-scores did not increase from TR of 2000ms and 1000ms at VV of $2 \times 2 \times 2 \text{ mm}^3$. At VV of $2 \times 2 \times 2 \text{ mm}^3$ and these TRs, the distributions of Z-scores seemed to have been too widespread due to the high physiological noise levels for the effect of increased SNR efficiency to be observed. In contrast, at TR of 500ms with less physiological noise contribution, the effect became apparent. Consistently, at each VV, the effect of increasing

SNR efficiency became apparent at TRs with similar $tSNR$ values, where the physiological noise level is assumed to be similar. $tSNR$ at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and TR of 1000ms was comparable to that of 500ms at $2 \times 2 \times 2 \text{ mm}^3$, which accounts for the Z-scores plateauing at the higher spatial resolution while they were still increasing at the lower spatial resolution.

Our results show that $\% \Delta S$ and decoding performance increased with temporal resolution only at the higher spatial resolution. The physiological noise level at the lower spatial resolution was again too high for the effect of temporal resolution to be observed. Supportively, the physiological noise level was nearing its limit to maintain thermal noise dominance at VV of $2 \times 2 \times 2 \text{ mm}^3$ and TR of 500ms, as the $tSNR$ only increased significantly up to VV of $3 \times 3 \times 3 \text{ mm}^3$ (up to $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ if $p < 0.01$).

4.2. Extension of characteristic spatiotemporal pattern of M1 and SMA BOLD activation to voluntary lower-limb motor cognition

The somatotopy of the human M1 has been studied extensively and it is well-established that the lower-limb joints are represented contralaterally in the dorsomesial region (Newton et al., 2008; Penfield and Boldrey, 1937). It is also well established that the SMA is involved in higher-order motor cognition, such as movement preparation and planning, and its involvement has been observed during both upper and lower limb movements (Kapreli et al., 2006; Luft et al., 2002; Newton et al., 2008; Sahyoun et al., 2004). Fittingly, the onset of activation in SMA during voluntary upper-limb movements putatively precedes that of M1. Such characteristic spatiotemporal dynamics of these two cortical regions has been readily detected during upper-limb movements using fMRI (Cunnington et al., 2003; Cunnington et al., 2006; Weiske et al., 2001). The current study extends these characteristic spatiotemporal dynamics of BOLD activation between SMA and M1 to unilateral ankle dorsiflexion.

Robust activations were also observed across a diffuse motor network of posterior parietal cortex (PPC), primary somatosensory cortex (S1), prefrontal cortex (PFC) and premotor area (PM) (Appendix B). However, to ensure that the sensitivity measures were calculated from congruent regions across resolutions and participants, the significant activation maps were masked with subject and imaging parameter specific mROI masks encompassing M1 and SMA.

4.3. Potential applications and implications

We demonstrate the feasibility of functional imaging at: (1) a fast temporal resolution of 500ms; (2) spatial resolutions finer than some cortical gray matter thicknesses (~2.79mm in M1; Butaman & Floeter, 2007) in all directions (i.e., 1.5mm isotropic voxels); (3) with a large enough coverage to encompass key neural networks; and (4) with robust BOLD sensitivity. Functional imaging in such conditions offers obvious advantages and applications for investigating complex neural functions.

At large, we aim to use high resolution 7T-fMRI to determine and improve the suitability of invasive motor-restorative BCI treatments at the individual level. Considering this goal, it would be ideal to understand the spatiotemporal dynamics of BOLD activity underlying complex cognitions at the highest possible resolution. For example, precisely identifying the locations of robust activation during higher-order motor cognitions and essential cognitive functions could improve the efficacy of future treatments by more accurately defining the target electrode implantation site and which critical neural regions to avoid.

We plan to presurgically simulate one's ability to control invasive BCIs as accurately as possible using fMRI, which could form a part of criteria to determine one's suitability for an invasive BCI treatment. Note that this requires optimizing acquisition parameters for the

accuracy of fMRI-based decoding performance estimating the electrophysiology-based decoding performance, not for the fMRI-based decoding performance itself. Considering this, an ideal time-course of fMRI-based decoding performance should mirror that of the haemodynamic response. This would more likely occur at a higher temporal resolution, as it provides more information per unit time (Chen et al., 2015) and offers a finer decoding window. Consistently, there was a considerable lag of sustained decoding performance long after the haemodynamic response had subsided in the current study (Figure 4b), which may falsely estimate one's ability to control invasive-BCIs. However, when retrospectively reducing the decoding window to the length of each respective TR, the time-course of decoding performance resembled the hemodynamic response more closely (Appendix C). Furthermore, prior knowledge about the spatiotemporal dynamics of a given signal is integral for optimizing feature selection for a valid classifier training (LeCun et al., 2015; Lotte et al., 2007; Nicolas-Alonso and Gomez-Gil, 2012).

The benefits of fMRI at ultra-high field strengths are maximized at adequately high spatial resolutions with thermal noise dominance (Triantafyllou et al., 2005; van der Zwaag et al., 2009). Fittingly, high spatial resolution is the familiar theme across innovative ultra-high field fMRI studies revealing exciting information about the human brain; such as cortical laminar-specific activity (Huber et al., 2015; Polimeni et al., 2010), millimeter scale localization of fMRI to electrophysiological signals (Siero et al., 2014), the illusive phenomenon of initial dip (Yacoub et al., 2001b), and orientation columns in the human visual cortex previously undetected by other imaging modalities (Yacoub et al., 2008). The current study compliments this theme by demonstrating that the temporal resolution dependent increase in BOLD sensitivity is also best realized at high spatial resolutions. The lack of improvements in overall BOLD sensitivity at the lower spatial resolution suggest that high spatial resolutions may even be necessary to yield significant benefits over the lower

field strength fMRI, which has been highly optimized over decades in clinical settings. Hence, the field's growing interest and efforts to simultaneously improve fMRI's spatial and temporal resolution are welcomed from a researcher's point of view – especially the substantial efforts to improve a familiar and robust sequence of GE-EPI.

Indeed, it would have been impossible to achieve the highest resolutions and current coverage used in this study using GE-EPI without the recent developments in accelerated imaging methods (Griswold et al., 2002; Moeller et al., 2010; Pruessmann et al., 1999; Setsompop et al., 2012; Sodickson and Manning, 1997). We show that maximizing the benefits of 7T requires the use of both parallel and multiband acceleration techniques to simultaneously push the limits of spatial ($1.5 \times 1.5 \times 1.5 \text{ mm}^3$) and temporal resolution (500ms) for functional network imaging with adequate coverage. The GRAPPA parallel image reconstruction (Griswold et al., 2002) used in this study allowed for a three times shorter TE which reduced SNR loss due to T_2^* effects and also allowed more slices to be acquired per unit time. When combined with the multiband acceleration (Blaimer et al., 2006), almost nine times more images per unit time could be acquired without compromising coverage and with minor compromise in image quality.

The image quality losses stemmed from the SNR loss, which is known as the g-factor penalty. Indeed, the g-factor penalty is what ultimately limited the current temporal and spatial resolution and coverage. With 32-receive coils, the image quality deteriorated beyond usability using higher acceleration factors and the same coverage due to limitations in coil sensitivity (data not shown). However, great strides at reducing the g-factor penalties have been made recently (Moeller et al., 2010; Setsompop et al., 2012) and its continued trajectory depicts a promising future of ultra-high spatial and temporal resolution functional imaging of the whole human brain.

4.4. Caveats

In the current study, the higher resolution images were acquired first and the acquisition order was kept consistent for all but the first participant. This was due to reoccurring, unknown scanner crashes that started during the third session. Given our main concerns with the high resolution images, they were acquired preferentially. While it is conceivable that this may have biased the results, this concern was dismissed given the favourable characteristics of the current experimental design. The simplicity of the task and the short durations of active blocks and total experiment time should have minimized practice and habituation effects due to minimal cognitive load (Constable and Spencer, 2001). Further, randomized condition orders and a long delay (~10min) between the two sets of motor tasks further diminished our concerns. Finally, the lack of differences in the volume of significant activation across TRs at both spatial resolutions and $\% \Delta S$ across TR at the lower spatial resolution suggested for this concern to be dismissed.

Given the short TRs and thin slice thickness used in the current study, one may be concerned about the inflow effect having biased the results. However, the smaller flip angles should have entailed less inflow effect from non-excited upstream blood entering the imaging slice by reducing T_1 -weighting (Gao and Liu, 2012; Gao et al., 1996). At 7T, the inflow effect from venous blood was thought to be minimal given the highly diminished intravascular signal contribution implied by a considerably short venous blood T_2^ (Duong et al., 2003). Inflow effects from arterial blood may have potential to bias the results, however we believe that it was minimal as the fMRI activations were observed mainly in the most superior slices. In the steady state, inflowing spins into the superior slices would have been saturated by excitation in the more inferior slices. Further, the use of multiband acceleration should have further diluted this effect (Howseman et al., 1999).*

Lastly, as highlighted throughout the discussion, our recommendation to increase the temporal resolution at high spatial resolutions considers the inherent constraint on the achievable resolutions implied by the minimum coverage required to encompass a neural network. In the current study, ~30mm was determined to be the minimum coverage needed to image the frontoparietal visuomotor network. Using a combination of multiband and parallel imaging acceleration techniques, 500ms was the fastest achievable temporal resolution at the spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ to ensure this coverage without compromising image quality significantly.

However, in instances where coverage is not essential (e.g., cortical layer imaging), higher spatial resolutions can readily be achieved at 7T, even at the sub-millimeter level (Muckli et al., 2015). It is likely that the beneficial effects of increasing the temporal resolution will eventually reach a limit with infinitely increasing spatial resolutions, as there will be a point where the level of signal will reduce below that of overall noise. Future studies should investigate such saturation point as it could determine the ultimate temporal and spatial precision that the neurovascular coupling can be studied using fMRI.

5. Conclusion

We demonstrated that at a high spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$, the observed BOLD contrast and decoding performance increased with temporal resolution without any compromises in Z-scores and volume of activation. This was despite the expected tSNR decrease due to T_1 -relaxation effects. These findings suggest that overall BOLD sensitivity can be increased with temporal resolution, given an adequately high spatial resolution with minimal physiological noise level. Importantly, we show that this sensitivity improvement could be extended to an fMRI application such as Brain-Computer Interfaces. These results show promising outlooks for the use of high-resolution ultra-high field fMRI in both research

687 *and clinical settings. Further, our results highlight the importance of optimizing acquisition*
688 *parameters specifically for the purpose of a given study to maximize the benefits of ultra-high*
689 *field fMRI.*

Accepted manuscript

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Appendix A. Voxel coordinates of common regions of significant activation during ankle dorsiflexion tasks in MNI space

Cluster Center of Gravity Coordinates

<i>Imaging parameters</i>			<i>LA>RA</i>			<i>RA>LA</i>		
<i>VV (mm³)</i>	<i>TR (ms)</i>	<i>Smoothing (mm; FWHM)</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>
<i>1.5x1.5x1.5</i>	<i>500</i>	<i>0</i>	<i>81</i>	<i>100</i>	<i>142</i>	<i>95</i>	<i>86</i>	<i>137</i>
<i>1.5x1.5x1.5</i>	<i>500</i>	<i>2</i>	<i>81</i>	<i>99</i>	<i>141</i>	<i>95</i>	<i>88</i>	<i>137</i>
<i>1.5x1.5x1.5</i>	<i>500</i>	<i>4</i>	<i>82</i>	<i>96</i>	<i>141</i>	<i>97</i>	<i>86</i>	<i>137</i>
<i>1.5x1.5x1.5</i>	<i>1000</i>	<i>0</i>	<i>83</i>	<i>94</i>	<i>142</i>	<i>99</i>	<i>92</i>	<i>139</i>
<i>1.5x1.5x1.5</i>	<i>1000</i>	<i>2</i>	<i>84</i>	<i>93</i>	<i>141</i>	<i>97</i>	<i>92</i>	<i>139</i>
<i>1.5x1.5x1.5</i>	<i>1000</i>	<i>4</i>	<i>83</i>	<i>94</i>	<i>142</i>	<i>98</i>	<i>91</i>	<i>139</i>
<i>1.5x1.5x1.5</i>	<i>2000</i>	<i>0</i>	<i>83</i>	<i>95</i>	<i>140</i>	<i>95</i>	<i>88</i>	<i>140</i>
<i>1.5x1.5x1.5</i>	<i>2000</i>	<i>2</i>	<i>82</i>	<i>93</i>	<i>139</i>	<i>97</i>	<i>87</i>	<i>137</i>
<i>1.5x1.5x1.5</i>	<i>2000</i>	<i>4</i>	<i>80</i>	<i>88</i>	<i>138</i>	<i>98</i>	<i>92</i>	<i>139</i>
<i>2x2x2</i>	<i>500</i>	<i>0</i>	<i>84</i>	<i>99</i>	<i>139</i>	<i>100</i>	<i>87</i>	<i>141</i>
<i>2x2x2</i>	<i>500</i>	<i>2</i>	<i>81</i>	<i>99</i>	<i>139</i>	<i>99</i>	<i>85</i>	<i>140</i>
<i>2x2x2</i>	<i>500</i>	<i>4</i>	<i>82</i>	<i>99</i>	<i>139</i>	<i>101</i>	<i>86</i>	<i>140</i>
<i>2x2x2</i>	<i>1000</i>	<i>0</i>	<i>83</i>	<i>92</i>	<i>138</i>	<i>97</i>	<i>91</i>	<i>141</i>
<i>2x2x2</i>	<i>1000</i>	<i>2</i>	<i>83</i>	<i>94</i>	<i>137</i>	<i>97</i>	<i>93</i>	<i>141</i>
<i>2x2x2</i>	<i>1000</i>	<i>4</i>	<i>85</i>	<i>93</i>	<i>140</i>	<i>97</i>	<i>91</i>	<i>140</i>
<i>2x2x2</i>	<i>2000</i>	<i>0</i>	<i>85</i>	<i>90</i>	<i>139</i>	<i>96</i>	<i>90</i>	<i>138</i>
<i>2x2x2</i>	<i>2000</i>	<i>2</i>	<i>85</i>	<i>91</i>	<i>139</i>	<i>97</i>	<i>90</i>	<i>139</i>
<i>2x2x2</i>	<i>2000</i>	<i>4</i>	<i>85</i>	<i>92</i>	<i>140</i>	<i>97</i>	<i>90</i>	<i>138</i>

VV=Voxel Volume; TR=Repetition Time; FWHM=Full Width Half Maximum; LA>RA=Left Ankle; RA>LA=Right Ankle

Appendix B. Regions of significant activation across nine participants at the group level without any masking, for the contrasts of LA>RA (red) and RA>LA (blue), and Left prompt>rest (green) and Right prompt>rest (violet) in MNI space at VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and TR of 500ms ($Z > 2.3$, $p < 0.05$, clusterwise corrected). Highly lateralized M1 activation was observed during the execution blocks. Diffuse bilateral activation was observed during each prompt blocks in the intraparietal area, supplementary motor area, and lateral prefrontal cortex. Contralateral activation was observed in the superior parietal cortex during each prompt blocks.

Appendix C. (Top row) Average time-courses of normalized percent signal change and (Bottom row) average decoding performance at various time points with a decoding window equal to TR, in significant voxels during prompt and execution blocks in SMA and M1, respectively. The vertical solid blue lines denote the start of prompt block, and the red solid line depicts the start of movement execution block. All shadings denote the standard error across participants.

Appendix D. The effect of increased sampling rate on observed percent signal change ($\% \Delta S$) was simulated. The curves plot the voxel, trial and participant averaged $\% \Delta S$ from images acquired at spatial resolution of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ and temporal resolution of 500ms (left), downsampled to 1000ms by subsampling every 2nd data point (middle) and 2000ms by subsampling every 4th data point (right) for nine participants. The shadings denote standard error across participants. The BOLD time-courses were extracted from all significant voxels for all four contrasts within the mROI from the Task fMRI analysis acquired at TR of 500ms and VV of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$. The data was subsampled to derive the 1000ms and 2000ms data. The data was averaged across voxels. The range of normalized percent signal change ($\% \Delta S$) was calculated for each trial. These values were averaged across trials then compared across the temporal resolution at the participant level. A series of Wilcoxon signed-rank tests revealed a significant increase in $\% \Delta S$ to temporal resolution of 500ms (mean $\% \Delta S \pm \text{SE}$ across participants; $7.51 \pm 0.60\%$) from 1000ms ($7.27 \pm 0.59\%$) and 2000ms ($6.79 \pm 0.56\%$), and to 1000ms from 2000ms (all $p < 0.01$).

Appendix E. Regions of significant activation for the contrasts of LA>RA (red) and RA>LA (green) in M1, and prompt>rest (blue) in SMA for in slices 5, 9, 13 and 19 for all participants overlaid onto the multiband functional images. The yellow box on the right illustrates the approximate coverage achieved with all 21 slices, with the raw functional image in blue overlaid on to the high-resolution T₁-weighted anatomical image.

Appendix F. Effect of repetition time on signal intensity. The preprocessed accelerated GE-EPI images acquired at various repetition times for representative participant 1 are presented. All imaging acquisition parameters were identical except the repetition time and flip angle. All images were thresholded with the lower limit of 0 and upper limit of 2000. The signal intensity values at voxel coordinates 74, 74, 10 (x, y, z) are displayed above the images.