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1 **Functional Cerebral Blood Volume Mapping with Simultaneous Multi-Slice Acquisition**

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16

17 Running Title: CBV mapping with SMS VASO

18

19 The body of the text contains 5224 words (with additional 1711 words in references)

20 **Highlights:**

- 21 • fMRI with CBV-mapping is combined with a simultaneous multi-slice readout.
- 22 • FOV is increased up to a factor of 4 to enable near whole-brain coverage.
- 23 • High SNR allows high-resolution imaging up to $1 \times 1 \times 1.2 \text{ mm}^3$.
- 24 • Higher specificity to GM tissue of CBV-fMRI compared to GE-BOLD is confirmed.

25

26 **Abstract**

27 The aim of this study is to overcome the current limits of brain coverage available with
28 multi-slice echo planar imaging (EPI) for vascular space occupancy (VASO) mapping. By
29 incorporating simultaneous multi-slice (SMS) EPI image acquisition into slice-saturation slab-
30 inversion VASO (SS-SI VASO), many more slices can be acquired for non-invasive functional
31 measurements of blood volume responses.

32 Blood-volume-weighted VASO and gradient echo blood oxygenation level-dependent (GE-
33 BOLD) data were acquired in humans at 7 T with a 32-channel head coil. SMS-VASO was
34 applied in three scenarios: **A)** high-resolution acquisition of spatially distant brain areas in
35 the visuo-motor network (V1/V5/M1/S1); **B)** high-resolution acquisition of an imaging slab
36 covering the entire M1/S1 hand regions; and **C)** low-resolution acquisition with near whole-
37 brain coverage.

38 The results show that the SMS-VASO sequence provided images enabling robust detection
39 of blood volume changes in up to 20 slices with signal readout durations shorter than 150
40 ms. High-resolution application of SMS-VASO revealed improved specificity of VASO to GM

1 tissue without contamination from large draining veins compared to GE-BOLD in the visual
2 cortex and in the sensory-motor cortex.

3 It is concluded that VASO fMRI with SMS-EPI allows obtaining a reasonable three-
4 dimensional coverage not achievable with standard VASO during the short time period
5 when blood magnetization is approximately nulled. Due to the increased brain coverage
6 and better spatial specificity to GM tissue of VASO compared to GE-BOLD signal, the
7 proposed method may play an important role in high-resolution human fMRI at 7 T.

8 **Abbreviations:** BOLD = blood oxygenation level dependent; CBV = cerebral blood volume;
9 CNR = contrast-to-noise ratio; CSF = cerebrospinal fluid; Δ CBV = change in CBV; EPI = echo
10 planar imaging; fMRI = functional magnetic resonance imaging; GE = gradient echo; GM =
11 grey matter; MT = magnetization transfer; ROI = region of interest; SNR = signal-to-noise
12 ratio; SS-SI VASO = slice-selective slab-inversion VASO; TE = echo time; TI = inversion time;
13 TR = repetition time; VASO = vascular space occupancy.

14 **Keywords:** vascular space occupancy, SS-SI VASO, cerebral blood volume, simultaneous
15 multi-slice, multi-band, 7 Tesla MRI

16 1. Introduction

17 Functional MRI (fMRI) has revolutionized cognitive neuroscience research. The size of
18 fMRI voxels can now be reduced below one millimeter, approaching the size of
19 individual cortical layers or columns. Since conventional gradient echo (GE) BOLD fMRI
20 measures changes in brain activity only indirectly via blood oxygenation changes
21 (Bandettini, 2012), however, it is limited with respect to its quantifiability and its spatial
22 specificity.

23 It has been shown (Kim et al., 2013a) that fMRI based on cerebral blood volume (CBV)
24 can map changes of brain activity with better spatial localization than GE-BOLD signal,
25 and without contamination by remote draining veins. The most commonly used method
26 for non-invasive measurements of CBV changes in humans is vascular space occupancy
27 (VASO) (Lu et al., 2003). Similar to CBV mapping in animals based on injection of contrast
28 agents, CBV mapping with VASO in humans provides high functional specificity to activity
29 in neural tissue (Donahue et al., 2006; Huber et al., 2015; Lu et al., 2005). VASO is
30 particularly attractive at high fields (7 T) due to the increase in image signal-to-noise
31 ratio and the longer blood T_1 relaxation time, which approaches the vasculature refill
32 time (Huber et al., 2014c). However, VASO requires image acquisition after an inversion
33 pulse at the blood magnetization nulling time of approximately $T_1 \times \ln(2)$. Thus, if multiple
34 consecutive slices are acquired after each inversion, they end up with different inversion
35 times (TI), limiting the brain coverage of this method. This is especially problematic at
36 high resolutions that require acquisition of relatively long echo trains.

1 The acquisition time window and the maximum acquisition duration are usually chosen
2 such that the uncertainty in the blood nulling time $\Delta T_1 \times \ln(2)$ is smaller than the variation
3 of the imaging time ΔT (Lu et al., 2004; Scouten and Constable, 2007). Considering that
4 the variation of blood T_1 with oxygenation state and haematocrit is in the order of 200
5 ms (Grgac et al., 2012; Rane and Gore, 2013; Zhang et al., 2012), all VASO data should be
6 acquired within this corresponding time interval. This limits the number of slices that
7 can be acquired with conventional EPI to be not greater than five (Huber et al., 2014a;
8 Huber et al., 2014c; Scouten and Constable, 2007).

9 Previous studies suggest that VASO coverage can be increased by combining VASO spin
10 preparation with advanced readout techniques such as three-dimensional (3D) GRASE
11 (Donahue et al., 2009; Poser and Norris, 2007, 2009). However, the long acquisition time
12 required for 3D GRASE and the shorter tissue T_2 at high field strengths can induce
13 through-plane blurring due to T_2 decay. In high-resolution fMRI, the short T_2 can also
14 introduce limitations with respect to the echo-train length, the number of acquired
15 slices, or spin echo (SE) BOLD signal contamination in VASO. This can be improved by
16 shortening the acquisition window, i.e., by shortening the echo-train length, by means of
17 in-plane parallel imaging. However, the considerable k-space undersampling with high
18 parallel imaging acceleration factors incurs losses in signal-to-noise ratio (SNR).
19 Furthermore, the numerous refocusing radiofrequency (RF) pulses can introduce
20 unacceptable additional energy deposition in sequences limited by specific absorption
21 rate (SAR) restrictions.

22 Alternatively, VASO coverage can be increased by combining VASO spin preparation with
23 multi-shot 3D readout strategies (Cretti et al., 2013; Hua et al., 2013). However, since in
24 this acquisition scheme different parts of k-space are acquired after separate excitation
25 pulses, only the k-space center is acquired at the blood-nulling time. This implies that
26 the high spatial frequencies (outer k-space lines, respectively) will be weighted by blood
27 flow effects in addition to the weighting from blood volume changes, which can
28 introduce inaccuracies in high-resolution fMRI.

29 Recently, simultaneous multi-slice imaging (SMS) with multi-band (MB) excitation was
30 developed to boost the brain coverage of data acquisition within a given acquisition
31 period (Feinberg et al., 2010; Moeller et al., 2010; Setsompop et al., 2012a). The use of
32 SMS-EPI can multiply the number of acquired slices during the acquisition window in
33 VASO experiments. In addition, it has been shown that the application of SMS-EPI can be
34 advantageous to overcome brain coverage limitations in ASL (Feinberg et al., 2013;
35 Ivanov et al., 2014; Kim et al., 2013b; Wang et al., 2015).

36 The purpose of this study is to implement and evaluate high-resolution functional
37 imaging with VASO and BOLD contrast using SMS-EPI for concurrent imaging of CBV and
38 oxygenation level.

1 This study focuses on the most important limitations of VASO-fMRI: the challenges to
2 simultaneously acquire enough imaging slices to cover multiple brain areas, and to
3 increase the slice resolution within an extended brain region. The novel VASO sequence
4 is applied in three experimental setups: **A)** high-resolution acquisition of distant brain
5 areas in the visuo-motor network (V1/V5/M1/S1); **B)** high-resolution acquisition of an
6 imaging slab covering the entire M1/S1 hand region; **C)** low-resolution acquisition with
7 near to whole-brain coverage.

8 **2. Materials and Methods**

9 **2.1. MR sequence**

10 MRI data were acquired with ten healthy right-handed participants (age 22-29 years).
11 All procedures were approved by the Ethics Committee of the University of Leipzig.
12 Informed written consent was given by all volunteers. SMS-SS-SI VASO was
13 implemented on a MAGNETOM 7T scanner (Siemens Healthcare, Erlangen, Germany)
14 in IDEA. For RF transmission and reception, a single-channel-transmit/32-channel-
15 receive head coil (Nova Medical, Wilmington, MA, USA) was used. Functional data
16 were acquired using an SMS two-dimensional (2D) single-shot EPI readout. The timing
17 of magnetization preparation and interleaved acquisition of VASO and BOLD data is
18 schematically depicted in Fig. 1. Sequence parameters were: $T_{I1}/T_{I2}/TR =$
19 $1100/2600/3000$ ms, nominal excitation flip angle was $\alpha = 70^\circ\text{-}90^\circ$ dependent on the
20 head size and the corresponding variation of the transmit voltage within SAR limits,
21 across all functional experiments. The summation of multi-band sinc-pulses was
22 conducted with optimized phase schedules for minimizing peak RF power (Wong,
23 2012). VASO can be contaminated by inflow of non-inverted, especially, when blood T_1
24 is not much shorter than TR (Donahue et al., 2006). Such inflow effects can be
25 avoided, when the blood-nulling time is shorter than the time that blood needs to
26 arrive from the arteries in the neck to the micro vessels of the imaging slice (Huber et
27 al., 2014). Here, a $T_{I1} = 1100$ ms is chosen, which includes an additional leeway of 200
28 ms compared to the estimated arterial arrival time in the sensorimotor cortex
29 (Mildner et al., 2014). The blood nulling time was manipulated by means of an
30 adjusted inversion efficiency of 87% in a B_1 -independent manner by using a phase skip
31 of the RF field during inversion as described in (Huber et al., 2014c). The inversion
32 pulse shapes are based on the TR-FOCI pulse (Hurley et al., 2010). The efficiency of the
33 pulse was 94% (measured in pilot experiments). This means that 6% of the
34 magnetization is lost during the application of the pulse. The inversion pulse
35 amplitude was adjusted to have a minimum of $10\ \mu\text{T}$ down to the Circle of Willis
36 across all participants by used a transmitter voltage of 340 V. The overall energy
37 deposition of the sequence never exceeded $2.1\ \text{W/kg}$, according to the SAR estimation
38 of the vendor. The blood nulling time is calculated based on the assumed value of

1 blood $T_1 = 2100$ ms, following earlier VASO studies at 7 T (Huber et al., 2014a; Huber
2 et al., 2015; Huber et al., 2014c).

3 With increasing field strength, the positive BOLD signal change during neural
4 activation increasingly counteracts the negative VASO signal change. The GE-BOLD
5 effect typically has two components: intra-vascular and extravascular. At 7 T, the
6 extravascular BOLD dominates the intravascular BOLD by more than 90% (Donahue et
7 al., 2010; Uludağ et al., 2009). This extravascular BOLD contamination is considerably
8 larger than the desired VASO signal change and needs to be corrected for. In SS-SI
9 VASO, an interleaved, pair-wise acquisition of VASO and BOLD images is used to
10 distinguish between BOLD and VASO signal components of the resulting signal. When
11 the pure BOLD contrast contribution is known, the BOLD-contamination in the VASO
12 image can be factored out, as described earlier (Huber et al., 2014a). In short, both
13 BOLD and VASO time series are expected to have the same BOLD T_2^* -weighting but
14 different VASO T_1 weighting. Hence, when the voxel-wise ratio image between the
15 BOLD and the VASO images is formed, the T_2^* -weighting is canceled out. This provides
16 a BOLD-corrected VASO contrast. As long as both images are acquired with the
17 identical EPI module, the T_2^* -weighting cancels out, independent of TE and readout
18 duration. This BOLD correction mechanism relies on the assumption that changes in
19 BOLD weighting are slower than the time between consecutive image acquisitions (3 s
20 for a pair of VASO and BOLD). This means that any temporal dynamics of the BOLD signal
21 change faster than 3 s will not be corrected for. Furthermore, it assumes that
22 extravascular effects contribute much more to the BOLD response than intravascular
23 effects. In this correction scheme, BOLD contaminations are considered to be solely
24 based on changes in T_2^* . Hence, the applied correction scheme is assumed to account
25 for BOLD contaminations in all compartments of the vascular tree including arteries,
26 capillaries and veins inside and outside the GM tissue. This means that the BOLD-
27 correction is not expected to have any limitations with respect to spatial resolution.

28 All functional experiments consisted of one-minute blocks repeated 12 times. The
29 VASO sequence parameters concerning resolution, acceleration and position were
30 optimized for three specific cases described as follows:

31 **2.1.1. Experiment A: Two high-resolution slice groups**

32 Two slice groups were positioned to cover V1/V5 and M1/S1 in 6 out of the 10
33 participants, using the following sequence parameters: nominal resolution =
34 $0.97 \times 0.97 \times 1.1 \text{ mm}^3 - 1 \times 1 \times 1.5 \text{ mm}^3$, depending on the participant's brain
35 anatomy; no slice gaps; $2 \times 5 = 10$ slices; SMS factor = 2; field-of-view (FoV) shift
36 (CAIPI factor) = 1; GRAPPA factor = 3, segmented reference line acquisition; TE
37 = 34 ms. The maximal time difference of image acquisition to the blood nulling
38 time ΔT_I was 162 ms. This means that the first excitation pulse was applied 162

1 ms before the blood nulling time point and the last excitation pulse was applied
2 162 ms after the blood nulling time point as indicated in Fig. 1. The distance
3 between the centers of the two slice groups was 14 – 17 mm, depending on
4 tilting angle and the participants' anatomy. This distance refers to the gap
5 between the two yellow imaging slabs depicted in Fig. 2A. Partial Fourier
6 imaging was kept minimal with a factor of = 7/8. The fat saturation pulse flip
7 angle was set to 30°, assuming that most of the fat signal due to its short T_2
8 would be decayed during the EPI readout anyway, not leading to serious fat
9 artifacts. The functional paradigm consisted of three conditions: 20s rest, 20s
10 visual task with a high-contrast static star field, and 20 s visual task with a high-
11 contrast moving star field as in (Huk et al., 2002) with concurrent finger motion
12 during the star motion. The finger motion consisted of pinch-like movement
13 and touch of index finger, middle finger, ring finger, and little finger
14 (consecutively) towards and away from the thumb with a self-paced frequency
15 of approximately 0.25 – 0.75 Hz.

16 **2.1.2. Experiment B: Whole M1 coverage with high spatial resolution**

17 One slice group was positioned to cover the entire areas of M1/S1 in 6 out of
18 the 10 participants, with the following sequence parameters: nominal
19 resolution = $1 \times 1 \times 1.2 \text{ mm}^3$ – $1 \times 1 \times 1.5 \text{ mm}^3$, depending on the participant's
20 brain anatomy; 50% – 70% slice gap; 15 slices; maximal $\Delta T/1$ = 175 ms; SMS
21 factor = 3; FoV shift = 1/3; GRAPPA factor = 2 with FLEET (Chapman et al., 1987)
22 reference lines (Polimeni et al., 2015); TE = 33 ms. To minimize T_2^* -blurring,
23 partial Fourier imaging was not used (Huber et al., 2014b). The functional
24 paradigm consisted of unilateral finger-tapping (alternating 30-s rest vs. 30-s
25 tapping). The tapping task was identical to experiment A.

26 **2.1.3. Experiment C: Near whole-brain coverage with low spatial resolution**

27 20 slices were positioned to cover the brain in 6 out of the 10 participants with
28 the sequence parameters: nominal resolution = $3 \times 3 \times 3 \text{ mm}^3$; 50% slice gaps;
29 maximal, $\Delta T/1$ = 75 ms; SMS factor = 4; FoV shift factor = 1/3; GRAPPA factor = 2
30 with FLEET reference lines; TE = 14 ms, partial Fourier factor = 7/8. The
31 functional paradigm was identical to that of experiment A.

32 **2.1.4. Direct comparison of SMS-VASO with non-SMS-VASO**

33 In order to evaluate, whether the application of SMS imaging in VASO may
34 degrade the image quality, direct comparisons of SMS-VASO and non-SMS-
35 VASO were conducted. In three additional participants, the imaging protocols
36 described above (experiments A-C) were repeated without functional
37 stimulation along with a variant with SMS factor 1 (non-SMS) leaving all other
38 parameters the same. With the reduced acceleration in the non-SMS-VASO

1 case, only 20% to 50% of the imaging region could be covered compared to
2 SMS-VASO. Hence, not all ROIs could be compared (V1, V5, M1/S1). Here, the
3 sensory motor area was chosen as a region for comparison. I.e. the imaging
4 slices were positioned to cover the M1/S1 area with both protocols, with the
5 SMS-VASO and the non-SMS-VASO.

6 Note that experiment A uses the segmented GRAPPA reference line acquisition, while
7 experiment B and C use FLEET GRAPPA reference line acquisition. The GRAPPA
8 reference line acquisition scheme of choice was decided based on respective
9 susceptibility to B_0 -inhomogenities, appearance of GRAPPA-ghosts and tSNR
10 obtained in respective pilot experiments.

11 **2.2. Image reconstruction**

12 Image reconstruction was performed online on the scanner. The data with 7/8 partial
13 Fourier were zero-filled. Signals from the simultaneously acquired slices were first un-
14 aliased with an implementation of SplitSlice-GRAPPA with LeakBlock (Cauley et al.,
15 2014) and a 3x3 kernel, as distributed with the MGH blipCAIPI C2P (Setsompop et al.,
16 2012b)(<http://www.nmr.mgh.harvard.edu/software/c2p/sms>); this was followed by
17 the vendor's in-plane GRAPPA reconstruction (Griswold et al., 2002), using a 2x3
18 kernel. Finally, the complex coil images were combined using the vendor's
19 implementation of adaptive combine.

20 **2.3. Data analysis**

21 All MR images were motion corrected using SPM8 (Wellcome Department, University
22 College London, UK). Statistical analysis was done using FSL FEAT (Version 5.98)
23 (Worsley, 2001). One of the major goals of this study is to investigate the spatial
24 features of CBV and BOLD signal changes in brain areas that are already known to be
25 involved in the functional task. Therefore, the purpose of the statistical analysis is not
26 to isolate significantly activated areas from other brain areas, but to investigate the
27 range of Z-values within the ROIs. Hence, Z-value thresholds in statistical activation
28 maps are kept relatively low, minimizing false negative voxels despite increasing the
29 risk of false positive voxels. Statistical data were not thresholded by cluster size. In
30 order to estimate and eliminate BOLD contamination in the CBV-weighted data, the
31 VASO signal was corrected using the BOLD signal acquired interleaved, as in previous
32 studies (Huber et al., 2014c). In the evaluation of data from experiment B (thick high-
33 resolution imaging slab covering M1), missing signal from inter-slice gaps was linearly
34 extrapolated from adjacent slices to provide undistorted signal maps in the coronal
35 and sagittal orientations. No spatial smoothing was applied during any part of the
36 offline data analysis.
37

38 **3. Results**

3.1. Experiment A: Two slice groups covering V1, V5, M1, and S1

The results of SMS-VASO imaging of the visuo-motor network are depicted in Fig. 2. Maps of temporal SNR (tSNR) are depicted in Fig. 2A for one representative subject. It can be seen that the proposed method has enough tSNR to significantly detect strong activity changes in V1 and in the contralateral sensory motor cortex. The inter-subject average tSNR of the VASO and BOLD signal in grey matter (GM) ROIs is 16 ± 3 and 22 ± 4 , respectively. Indications of positive and negative activity changes in the ipsilateral sensory-motor region and in V5 are clearly visible, but not as robustly as in the contralateral sensory-motor region.

The contralateral M1 and S1 yielded significant signal increases during the unilateral finger motion task. The ipsilateral M1 shows a positive BOLD signal change and CBV increase, while ipsilateral S1 shows a negative BOLD and CBV decrease in all participants.

Black arrows in the lower slice of the results in Fig. 2A refer to fat signal artifacts, which most probably result from insufficient fat suppression. Since they are expected to be the same at every time point during the experiment, they can be considered negligible with respect to the functional results presented.

Fig. 2B depicts the reproducibility and stability of the results across participants. The average signal changes of the contralateral BOLD and VASO responses were $(2.3 \pm 0.5)\%$ and (-1.7 ± 0.5) ml/100ml respectively in M1 and $(2.9 \pm 0.4)\%$ and (2.0 ± 0.5) ml/100ml in S1, respectively. The average signal changes of the ipsilateral BOLD and VASO responses were $(1.8 \pm 0.5)\%$ and (-1.1 ± 0.4) ml/100ml, respectively in M1 and $(-1.6 \pm 0.4)\%$ and (1.2 ± 0.4) ml/100ml in S1, respectively.

It is worth pointing out that BOLD is inherently sensitive to task-correlated motion (Fig. 2; green arrows in participants 1 and 2) (Schulz et al., 2014), while any variations in the signal beyond functional T_1 changes are inherently suppressed in the BOLD-correction procedure (which involves taking the ratio of sequential images) in SS-SI VASO.

The average time courses of GE-BOLD and VASO response signals are depicted in Fig. 2C. V1 is sensitive to contrast changes, and is largely independent of the amount of motion in the visual presentation. V5, contralateral M1, contralateral S1, and ipsilateral M1 have an overall activation response during movements, while ipsilateral S1 has an overall deactivation response during unilateral movements. This is consistent with CBV and BOLD signal responses in previous studies (Huber et al., 2015). Following the BOLD and VASO time courses, it can be seen that there is no significant post-stimulus undershoot, even in V1. This is consistent with previous BOLD and VASO results using the same visual moving star field paradigm (Huber et al., 2014c), which shows a slightly different response shape compared to a more common

1 flickering checkerboard paradigm. It must be also noted that the occurrence of a
2 significant post-stimulus undershoot is highly dependent on the extent of the area of
3 interest (van Zijl, et al., 2012), and the inter-stimulus resting period used (Huber et al.,
4 2014d).

5 **3.2. Experiment B: High-resolution M1 coverage**

6 The results of SMS-VASO for high-slice-resolution imaging of an imaging slab spanning
7 across M1 are depicted in Fig. 3. The average tSNR (Fig. 3A) of VASO and BOLD signal
8 in GM ROIs of M1/S1 is 14 ± 2 and 24 ± 4 , respectively. The tSNR is sufficient to obtain
9 highly consistent and reproducible results across participants (Fig. 3B). The activity
10 pattern in contralateral and ipsilateral sensory motor cortex is very similar to the
11 results from experiment A (Fig. 2).

1 **Experiment C: Near whole-brain coverage acquisition**

2 The results of SMS-VASO for low-resolution acquisitions to cover nearly the entire
3 brain are depicted in Fig. 4. Average tSNR (Fig. 4A) of VASO and BOLD signal in GM
4 ROIs is 33 ± 6 and 57 ± 12 , respectively. The activity patterns are very similar across
5 participants (Fig. 4B), and they are consistent with the results of experiment A (Fig. 2).
6 The limited robustness in the detection of small negative response in ipsilateral S1 and
7 the small positive response in V5 might be a result of the partial voluming of GM with
8 white matter and cerebro-spinal fluid (CSF), or partial voluming of opposite responses
9 in M1/S1 at low resolution.

10 **3.3. Direct comparison of SMS-VASO with non-SMS-VASO**

11 The results of the direct comparison of SMS-VASO and non-SMS-VASO are depicted in
12 Fig. 5. The depicted tSNR maps show that there is no significant image quality
13 reduction, when applying SMS-VASO compared to non-SMS-VASO. The tSNR in the
14 M1/S1 region for SMS-VASO and non-SMS VASO was 18 ± 4 and 19 ± 4 for experiment
15 A, 15 ± 3 and 14 ± 4 for experiment B, and 33 ± 5 and 29 ± 4 for experiment C,
16 respectively. The negligible tSNR difference with and without SMS imaging is
17 consistent with previous studies. Setsompop et al. showed that the g-factor remains
18 around 1.0 for SMS imaging with CAIPI and SMS factors up to 3 (Setsompop, et al.,
19 2012).

20 **3.4. Summary of statistical numerical results of functional results**

21 The statistical Z-values within activated regions depicted in Figs 2-4 are summarized in
22 Tab. 1. The manually selected ROIs are V1, V5, and the contralateral side of M1. It can
23 be seen that the statistical Z-values are larger for BOLD compared to VASO. This is
24 consistent with the higher tSNR in BOLD compared to VASO.

25 **4. Discussion**

26 The results shown in Figs. 2 and 3 clearly demonstrate a major advantage of high-resolution
27 VASO. This methodology can distinguish different individual responses in neighboring but
28 distinct brain areas (e.g. ipsilateral S1 and M1), that cannot be separated with GE-BOLD,
29 with low-resolution fMRI, or when applying spatial smoothing (Stelzer et al., 2014).

30 **4.1. Other 3D imaging approaches**

31 Besides the combination of VASO with SMS acquisition, several advanced imaging
32 strategies have been proposed to increase the coverage of VASO (Lu et al., 2013).
33 These include MAGIC VASO (Lu et al., 2004), 3D GRASE VASO (Donahue et al., 2009;
34 Poser and Norris, 2009), HASTE VASO (Poser and Norris, 2007), multi-shot 3D turbo
35 field echo VASO (Hua et al., 2013), and multi-shot 3D TSE VASO (Cretti et al., 2013).
36 Compared with these previously suggested approaches for increasing the VASO

1 coverage, the proposed SMS acquisition is particularly beneficial for obtaining high
2 spatial resolution, because it can increase the coverage without increasing the
3 acquisition duration. For a further increase in SMS-VASO coverage, the technique
4 could be combined with the MAGIC VASO (Lu et al., 2004) approach, in which the
5 blood signal is forced to pass through zero multiple times by means of additional
6 inversion pulses during the acquisition. However, the SAR constraints of the
7 corresponding additional inversion pulses at high field strengths might limit its
8 application dependent on the efficiency of the hardware available. More research is
9 needed to determine the applicability of MAGIC VASO at high field strengths.

10 **4.2. Limitation by TR for vasculature refilling**

11 The proposed high tSNR of SS-SI VASO compared to the traditional VASO approach is
12 based on additional assumptions regarding the blood flow dynamics. For complete
13 nulling of once-inverted blood magnetization in SS-SI VASO, it is required that all the
14 blood within the imaging slice is refilled within one TR. It is estimated in the original
15 SS-SI VASO paper (Huber et al., 2014c) that it takes 1-1.5 s until the microvasculature
16 of a single slice is refilled with fresh blood. For a thicker imaging slab, the refilling time
17 is expected to be correspondingly longer. In order to avoid incomplete blood nulling in
18 the proposed SMS-SS-SI VASO method, we chose the TR to be minimally 3 s, giving the
19 blood enough time to refill the entire brain. With this sequence timing, the measured
20 changes in V1 are not different from the estimated changes in V1 in previous studies,
21 acquired with the same activation task but a single-slice implementation (Huber et al.,
22 2014c). This suggests that with the sequence timing used in this study, the acquisition
23 of more slices does not lead to additional violation of the refill condition.

24 **4.3. Effect of incomplete blood nulling**

25 There are two major sources of incomplete blood nulling in VASO. (i) Uncertainties in
26 blood T_1 , e.g. due to physiologic reasons, such as oxygenation level and inter-subject
27 variations in hematocrit. (ii) Variations in TR , due to technical reasons, e.g. the
28 consecutive acquisition of multiple 2D slices. It has been recently shown that the
29 difference between arterial blood T_1 and venous blood T_1 , and the influence of
30 moderate variations in hematocrit lies in the range of 100 – 200 ms (Grgac et al., 2012;
31 Rane and Gore, 2013). A sequence of up to five consecutive excitation pulses causes a
32 variation in blood-nulling time of the same order (75 – 175 ms). The corresponding
33 incomplete blood nulling can result in an error in the VASO signal change of up to 14%
34 relative to the total VASO signal change. This means that in the worst-case scenario,
35 the measured CBV change of 2.0 ± 0.5 ml/100ml in contralateral M1 might have an
36 additional source of uncertainty, to become 2.0 ± 0.5 (inter-subject standard
37 deviation) ± 0.28 (uncertainty in blood-nulling time) ml/100ml. Since the
38 corresponding bias of VASO quantification from slices acquired before blood nulling
39 and from slices acquired after blood nulling is opposite in sign, these biases are

1 believed to largely cancel each other out after averaging across ROIs and, thus, to
2 have no significant effect on the averaged results of this study.

3 **4.4. Signal change at cortical surface**

4 The VASO contrast at the cortical surface can suffer from artifacts arising from (i)
5 BOLD contaminations and (ii) dynamic changes in CSF volume (Lu et al., 2013) that
6 could complicate the interpretation of CBV changes at the cortical surface. While
7 conventional VASO contrast generation can suffer from these contaminations, they
8 have only a limited effect in the application of SS-SI VASO, as discussed in (Huber et
9 al., 2015). (i) Any extravascular BOLD contamination is corrected for in SS-SI VASO by
10 means of dynamic division by the interleaved-acquired BOLD signal. (ii) Contamination
11 of dynamic changes in partial volume from CSF can be minimized in SS-SI VASO by
12 manipulation of the steady-state CSF magnetization such that it has a positive phase
13 and a similar signal compared to GM. Hence, it is expected that the high GM tissue
14 specificity of SS-SI VASO is dominated by the sensitivity to microvascular vessels.

15 In two out of six participants, there are a few voxels clearly between the two sides of
16 the contralateral sulcus that show a positive VASO response, suggesting
17 vasoconstriction (participant 2 and 4 in Fig. 3). Such features have also been reported
18 by others, and have been interpreted as volume constriction of large draining veins
19 (Blockley et al., 2012) or neural inhibition (Trampel et al., 2013).

20 **4.5. Functional specificity**

21 Data given in Figs. 2 and 3 show that VASO fMRI can better delineate individual GM
22 territories, as compared with GE-BOLD which invariably shows largest activity
23 between the opposing GM banks of a sulcus. The higher spatial specificity of VASO to
24 GM tissue without contamination from independent of large draining veins can be
25 particularly rewarding when opposing GM banks of a sulcus comprise different nodes
26 of a brain network (e.g. M1 and S1). Where there is positive response in opposite GM
27 areas (e.g. contralateral M1/S1), the GE-BOLD signal of both areas is amplified by the
28 draining vein effect (Turner, 2002) to be maximal in larger veins above the cortical
29 surface (see purple inserts in Figs. 2 and 3).

30 In the case of positive and negative responses in opposing GM banks (e.g. ipsilateral
31 M1/S1), the mixing of deoxyhemoglobin changes arising from opposite responses on
32 opposite sides of the sulcus can result in an attenuated GE-BOLD signal (see blue
33 inserts in Figs. 2 and 3). For example, pial veins within the sulcus can drain both M1
34 and S1, and hence their BOLD signal might reflect a mixture of activity in both areas.
35 Such features, which have not previously been discussed in the literature, can make it
36 difficult to interpret the corresponding BOLD signal from opposite sides of the sulcus.
37 The higher specificity to brain tissue in VASO, avoids such limitations, and depicts
38 responses in opposing GM banks of the central sulcus independently.

1 **4.6. Response in the ipsilateral hemisphere**

2 Figs. 2 and 3 show that unilateral finger movement evokes a positive response in
3 ipsilateral M1, but a negative response in ipsilateral S1. This particular result has been
4 found to be highly dependent on stimulus paradigm and strength. While low force
5 (usually 5% of individual maximal voluntary contraction) has been shown to evoke a
6 negative BOLD response, and reductions in blood flow and metabolism in ipsilateral
7 sensori-motor ROIs, positive responses in ipsilateral M1 have been observed when
8 stronger forces and more demanding tasks are used (Dettmers et al., 1995).

9 **4.7. Magnetization transfer effects in SMS-VASO**

10 The application of off-resonant RF pulses in inversion recovery sequences such as
11 VASO, results in magnetization transfer (MT) effects. These MT effects can result in an
12 accelerated longitudinal relaxation mimicking a different T_1 . In the application of SMS-
13 VASO the (off-) resonant excitation pulses have increased RF amplitude and thus also
14 higher potential to induce MT effects. While there are significant MT effects in most
15 brain tissues, it has been shown that blood exhibits a very small MT effect due to its
16 low concentration of macromolecules (Wolff and Balaban, 1989; Balaban et al., 1991).
17 This means that while off-resonant RF pulses affect the tissue relaxation, blood
18 relaxation is not altered, leaving the blood nulling time unaffected. In fact, this unique
19 difference between blood and brain tissue regarding MT effects has been used to
20 actively enhance SNR in high field VASO experiments by means of additional high-
21 power MT pulses (Hua et al., 2009 and 2013). In conclusion, the additional MT effects
22 due to the multiband excitation pulses do not alter the blood nulling time and CBV
23 quantification, but are believed to result in a slightly larger GM signal and
24 corresponding SNR increase.

25 **4.8. Extensibility to lower field strengths**

26 While all experiments in this study were conducted at 7 T, its application might be
27 advantageous at 3 T as well. The shorter blood T_1 at lower field strengths (Zhang et al.,
28 2013), however, results in reduced signal gain applying SS-SI VASO as opposed to the
29 original VASO (Huber et al., 2014c). Additionally, the larger relative thermal noise
30 contribution at 3 T compared to 7 T can also be an additional constraint in going to
31 such high spatial resolutions at lower field strengths. The low-resolution approach of
32 experiment C, however, might be a useful tool for quantitative fMRI techniques, such
33 as calibrated BOLD, both at 3 T and 7 T. More research is necessary to evaluate the
34 combination of VASO and SMS imaging at 3 T.

35 **4.9. Other imaging modalities**

36 Spin echo (SE) BOLD fMRI has been suggested to have higher specificity to the
37 microvasculature (Uludağ et al., 2009) and its utility for laminar and columnar fMRI

1 has been demonstrated in animals (Goense et al., 2012; Harel et al., 2006; Zhao et al.,
2 2006) and in humans (Yacoub et al., 2005; Yacoub et al., 2008). However, it suffers
3 from much lower sensitivity, especially at high resolution (Yacoub et al., 2005), which
4 may limit the widespread application of the technique (Boyacioglu et al., 2014; Budde
5 et al., 2014; Harmer et al., 2012).

6 7 **5. Conclusion**

8 SMS-EPI has a major advantage in VASO fMRI by acquisition of more slices during the
9 short time period ΔT_I when blood magnetization is sufficiently nulled. Due to the
10 increased brain coverage and better localization specificity of VASO to GM tissue
11 compared to GE-BOLD signal, the proposed method can play an important role in high-
12 resolution fMRI at 7 T.

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32

33 **Tables:**

34 Tab. 1: Statistical Z-value results of functional experiments.

VASO	Experiment A		Experiment B		Experiment C	
	Mean	STD	Mean	STD	Mean	STD
V1 area	4.6	1.3	ROI not in FOV		6.7	1.2
MT area	3.7	1.2	ROI not in FOV		4.6	1.1
M1 area (contralateral)	3.7	0.5	5.5	2.2	8.0	3.2

35

BOLD	Experiment A		Experiment B		Experiment C	
	Mean	STD	Mean	STD	Mean	STD
V1 area	7.7	1.2	ROI not in FOV		9.5	1.3
MT area	4.5	1.8	ROI not in FOV		6.3	0.7
M1 area (contralateral)	7.2	1.4	9.7	2.3	10.5	3.1

36

1

2 **Figure captions:**

3 **Fig. 1: Magnetization preparation, readout, and sequence timing.**

4 Schematic depiction of one TR in the SMS-VASO sequence starting with the application of an
5 adiabatic inversion pulse. A phase skip is used to be in control of the inversion efficiency and
6 inflowing fast blood. The VASO images are acquired around the blood nulling time at $T11 =$
7 1.1 s after sequential transmission of multi-band RF excitation pulses. The multi-band factor
8 varies between 2 and 4 in this study (SMS-factor = 4 in figure). $\Delta T1$ denotes the deviation of
9 the theoretical blood nulling time. Dependent on the acquisition parameters it is $\Delta T1 = 75 -$
10 175 ms in this study. The phase-encoding and read gradients for the 2D-EPI acquisition are
11 accompanied with blipped-CAIPI gradients in slice direction for controlled aliasing of near
12 slices. In this study the corresponding FoV-shift factor was between 1 and 1/3 (here, FoV-
13 shift = 1/3). A second set of images is acquired at $T12 = 2.6$ s containing BOLD signal
14 weighting without CBV-weighting.

15 **Fig. 2: Results from experiment A: two slice groups during visuo-motor task.**

16 SMS-VASO results for high-resolution imaging of the visuo-motor network containing V1, V5,
17 M1, and S1. The left side of the figure refers to VASO-CBV sensitivity and the right side
18 refers to the interleaved acquired BOLD signal. **A** depicts the imaging slab orientation, tSNR
19 maps and the functional response of one representative subject. It can be seen, how the
20 insensitivity of VASO to large draining veins results in an improved specificity to GM tissue
21 compared to BOLD. The purple insets show how the activity clusters of VASO are confined to
22 the two GM banks of the central sulcus, while BOLD signal shows one connected blob only.
23 Also in V1, VASO activity patterns can delineate the cortex at the subarachnoid boundary
24 better compared to GE-BOLD (blue arrow). **B** depicts the stability of the results across four
25 participants. The higher specificity of VASO to GM tissue of M1 compared to GM tissue of S1
26 is visible consistently across participants. **C** depicts the corresponding time courses of BOLD
27 and VASO signal in ROIs of V1, M1, and S1. Note that VASO is a negative contrast and VASO
28 signal decrease is indicating CBV increase. Error bars refer to inter-participant standard
29 deviations.

30 **Fig. 3: Results from experiment B: High-resolution imaging of the entire M1/S1 region.**

31 SMS-VASO results for high resolution imaging of the sensory-motor cortex. The left side of
32 the figure refers to VASO-CBV sensitivity and the right side refers to the BOLD signal
33 acquired interleaved. **A** depicts the imaging slab orientation, tSNR maps and the functional
34 response of one representative subject. It can be seen how the insensitivity of VASO to large
35 draining veins results in an improved specificity to GM tissue compared to BOLD. Activity
36 clusters of VASO are confined to the two GM banks of the central sulcus, while BOLD signal
37 shows one connected blob only. Note that the high specificity of VASO to GM tissue
38 independent of large draining veins clearly reveals that M1 has a higher cortical thickness

1 compared S1, which can be useful in cortical segmentation. **B** depicts the stability of the
2 results across four participants. The higher specificity of VASO to GM tissue of M1 compared
3 to GM tissue of S1 is visible consistently across participants. Please note that unlike Fig. 2,
4 this Fig. does not contain visual areas. The color code is chosen, such that red and blue
5 stand for activation and deactivation during unilateral finger motion.

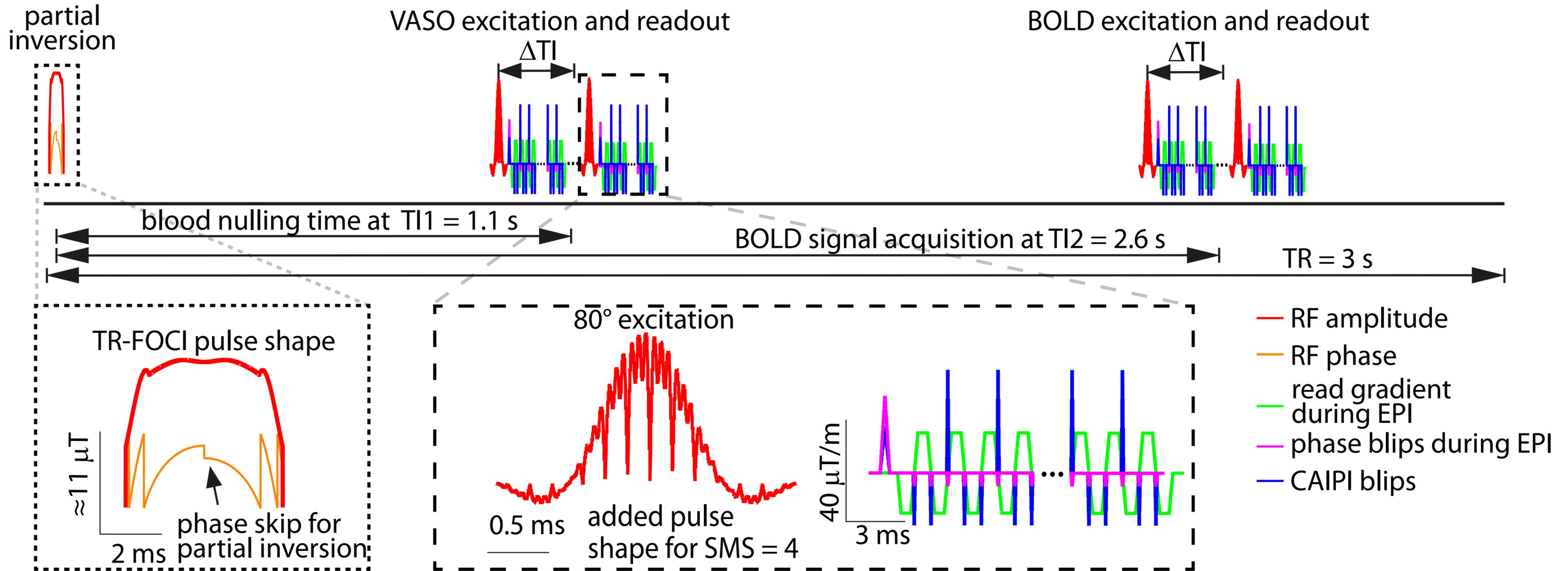
6 **Fig. 4: Results from experiment C: Near whole-brain coverage.**

7 SMS-VASO results for low-resolution near whole-brain coverage. The left side of the figure
8 refers to VASO-CBV sensitivity and the right side refers to interleaved acquired BOLD signal.
9 **A** depicts the imaging slab orientation, tSNR maps and the functional response of one
10 representative subject **B** depicts the stability of the results across four participants. Both,
11 SMS-VASO and BOLD can detect significant activity in V1, in V5 and the M1/S1 area across
12 participants.

13

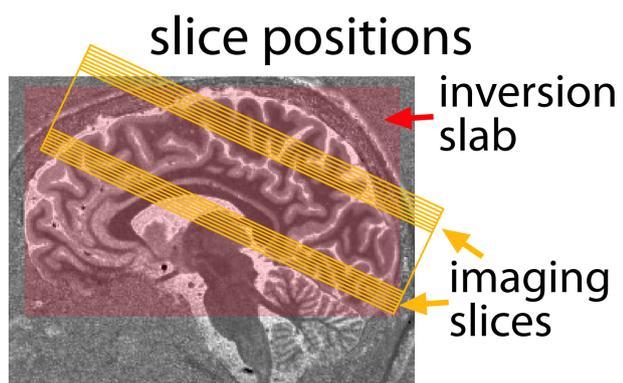
14 **Fig. 5: Direct comparison of SMS-VASO and non-SMS-VASO.**

15 tSNR results for all three experimental protocols (A-C) in three participants. tSNR maps with
16 and without SMS refer to the same in-plane acquisition scheme. There is no apparent loss of
17 image quality when applying SMS imaging compared to conventional single-band imaging.
18 With the application of blipped-CAIPI and the leakBlock unaliasing, the tSNR reduction is
19 below 15% in all protocols and there is no visible signal leakage between the simultaneously
20 acquired slices.



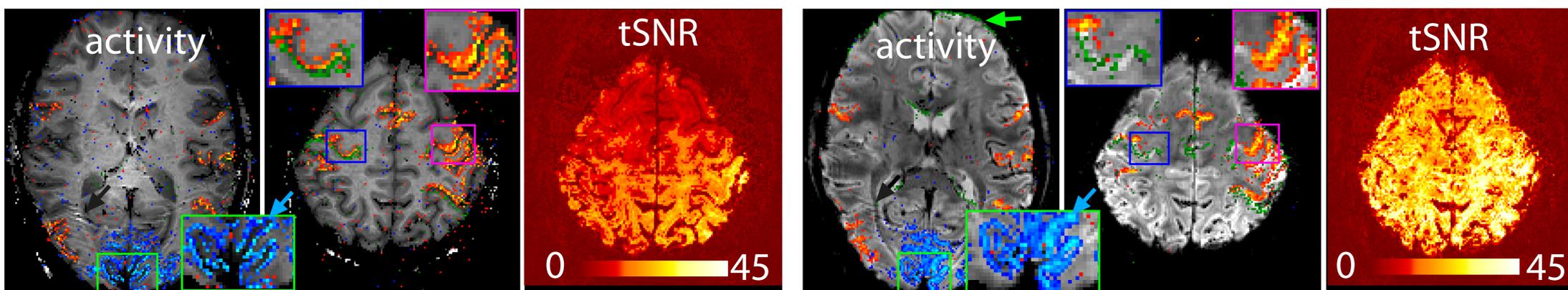
A representative participant

VASO

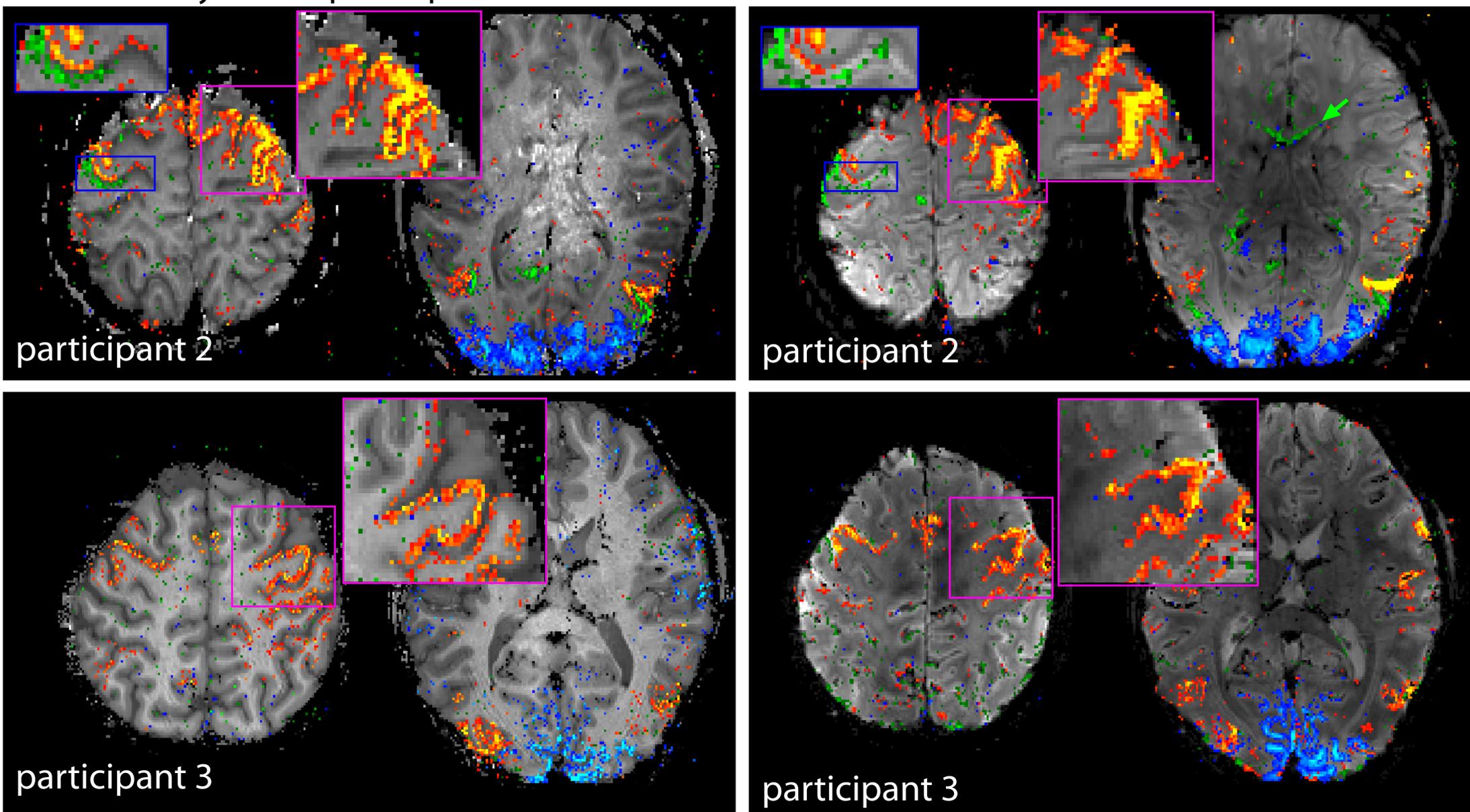


z-val	BOLD 3		static 12 3		motion 20 3		static 12	
	vs.	rest	7	1.7	vs.	static	8	1.7
	VASO 1.7						motion 8	

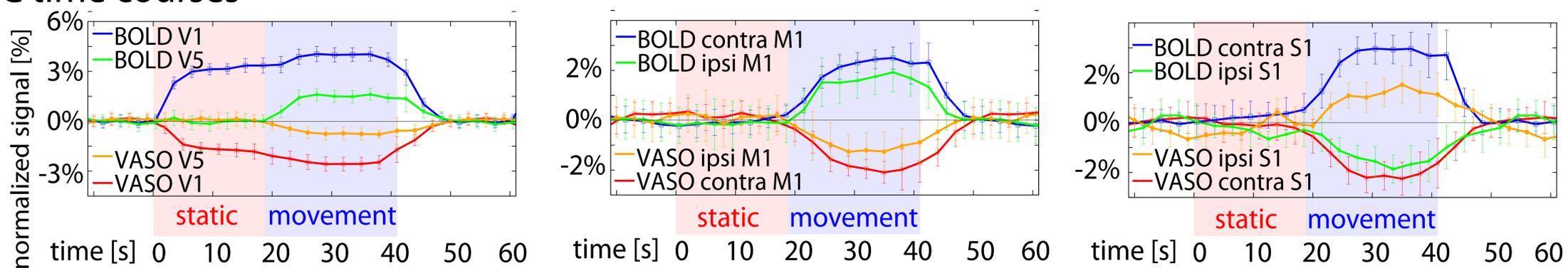
BOLD



B consistency across participants

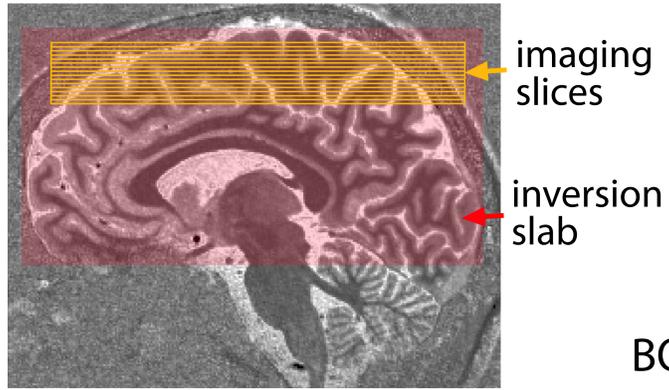


C time courses



A representative participant

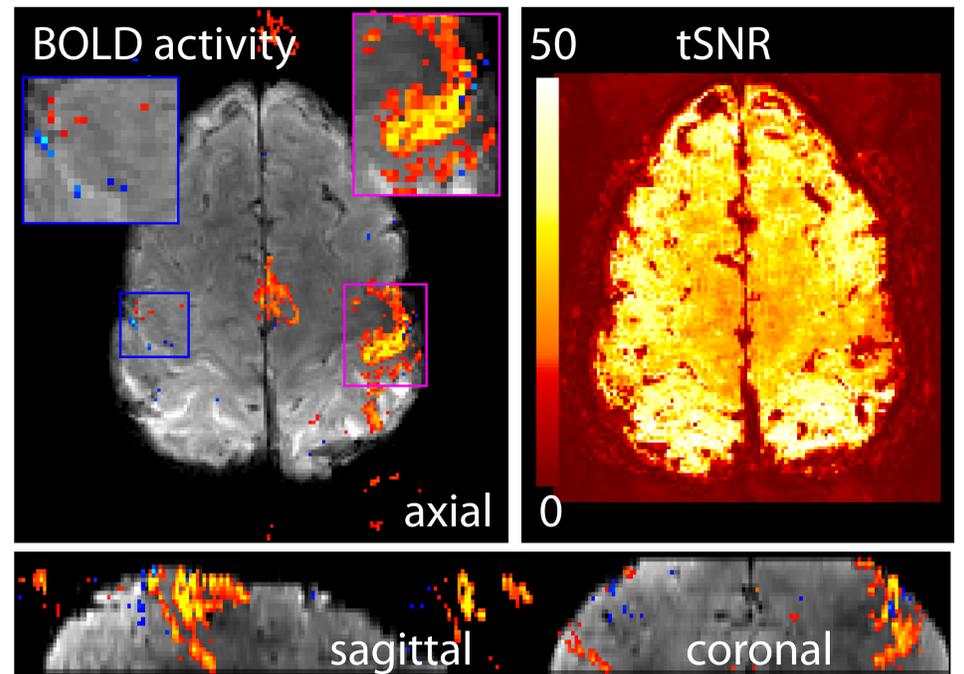
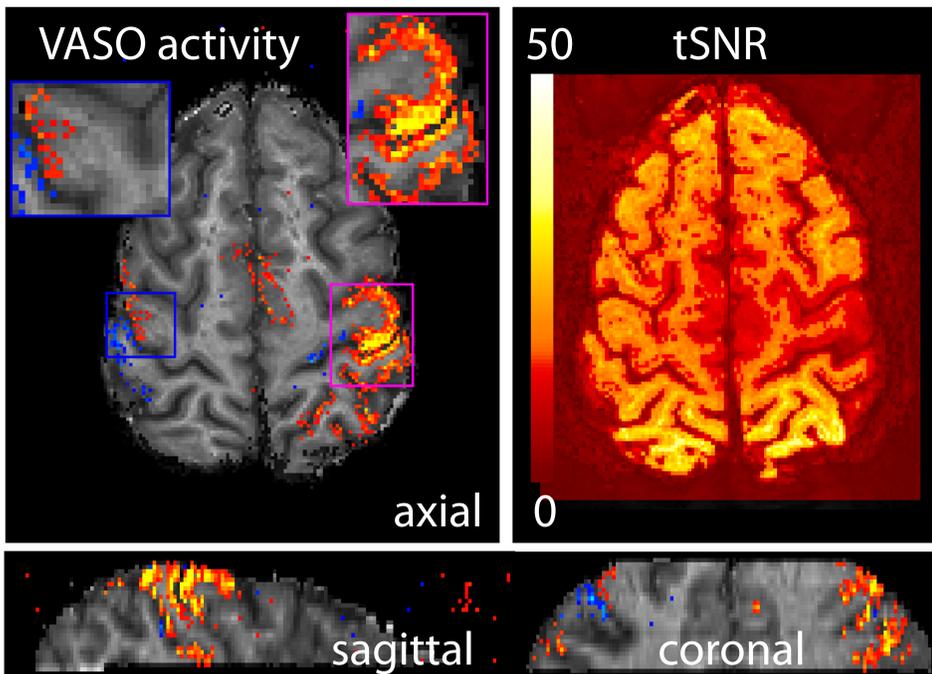
slice positions



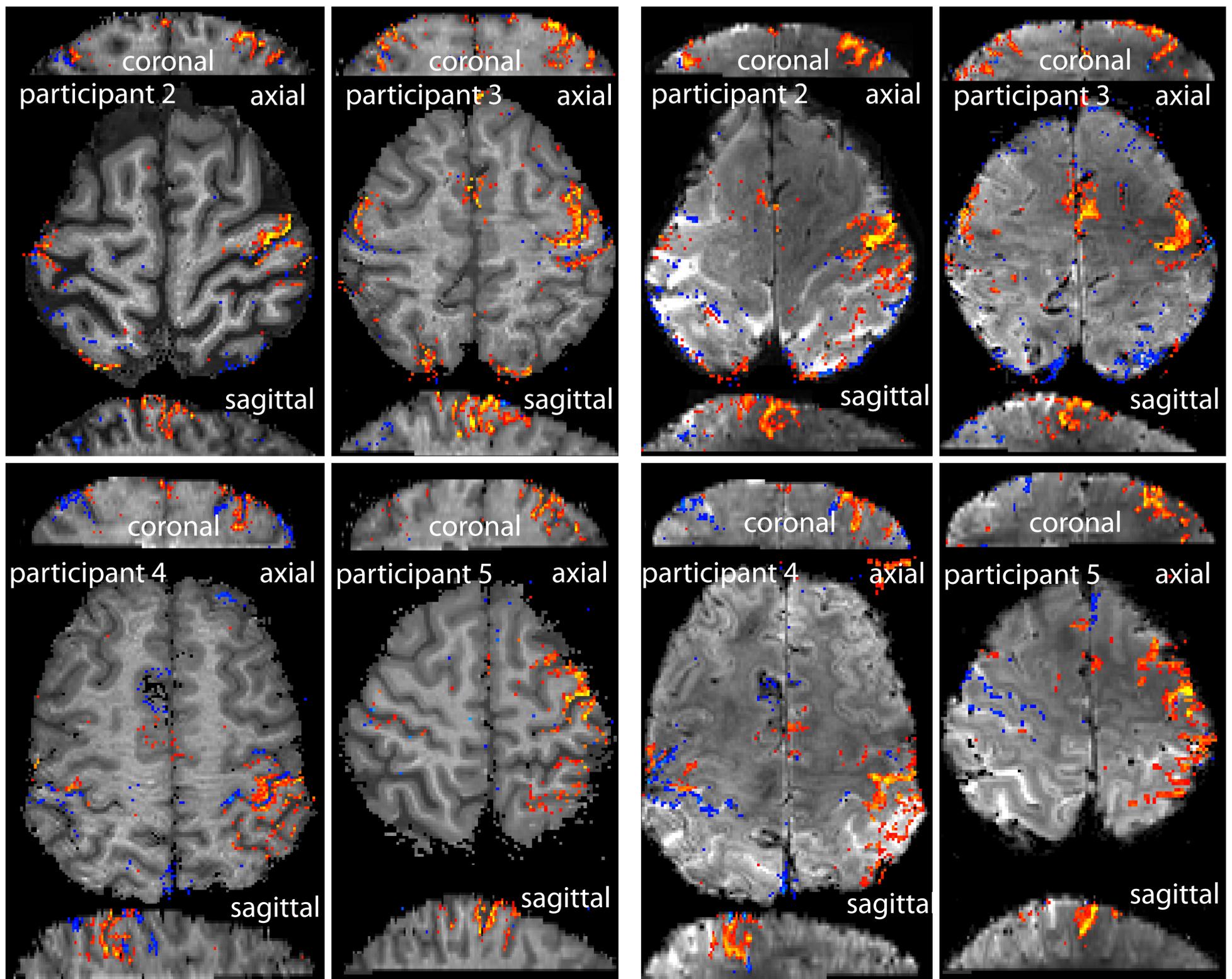
z-val	4	tapping	21	3	rest vs.	8
BOLD	2	vs. rest	9	2	tapping	5
VASO						

VASO

BOLD

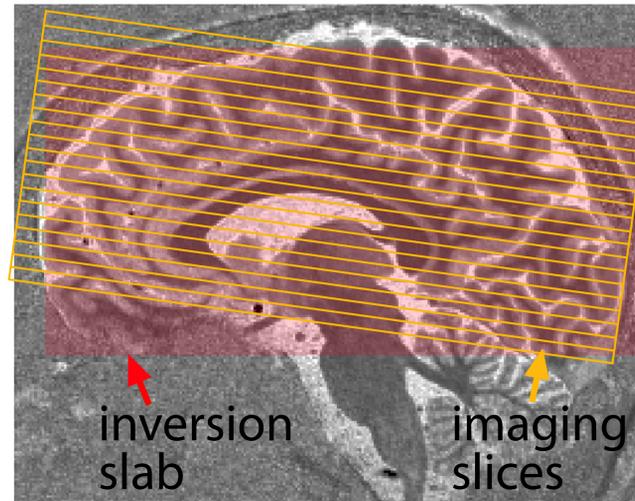


B consistency across participants



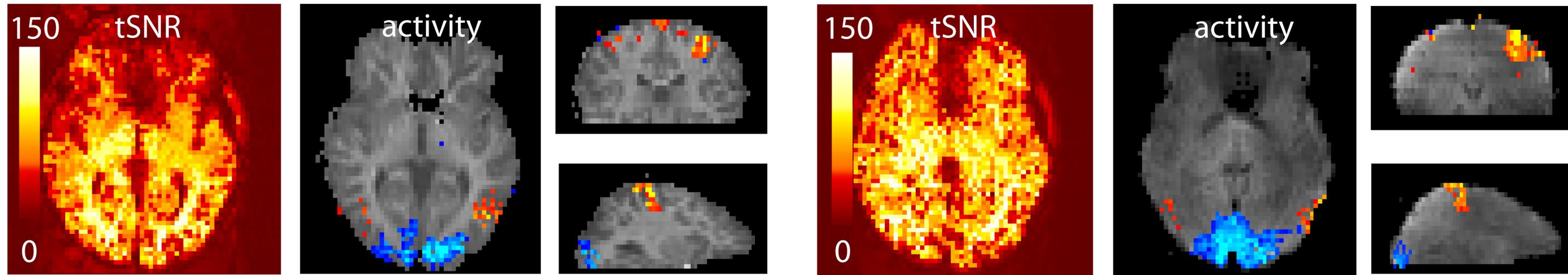
A representative participant

slice positions



VASO

BOLD



B consistency across participants

