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# 1 Estimates of cortical column orientation improve

## 2 MEG source inversion

3 **James J Bonaiuto<sup>1,2</sup>, Fardin Afdideh<sup>2,3</sup>, Maxime Ferez<sup>2,3</sup>, Konrad Wagstyl<sup>4,5</sup>, Jérémie Mattout<sup>2,3</sup>,**  
4 **Mathilde Bonnefond<sup>2,3</sup>, Gareth R Barnes<sup>5\*</sup>, Sven Bestmann<sup>5,6\*</sup>**

5 \*: joint last author

6 1) Institut des Sciences Cognitives Marc Jeannerod, CNRS UMR 5229, Bron, France

7 2) Université Claude Bernard Lyon 1, Université de Lyon, France

8 3) Lyon Neuroscience Research Center, Brain Dynamics and Cognition team, INSERM UMRS 1028, CNRS  
9 UMR 5292, Bron, France

10 4) University of Cambridge, Department of Psychiatry, Cambridge CB2 0SZ, UK

11 5) Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, University  
12 College London (UCL), London, WC1N 3BG, UK

13 6) Dept of Clinical and Movement Neuroscience, UCL Queen Square Institute of Neurology, University  
14 College London (UCL), London, WC1N 3BG, UK

15 **Corresponding author and Lead contact:** [james.bonaiuto@isc.cnrs.fr](mailto:james.bonaiuto@isc.cnrs.fr); @jbonaiuto

16

17 **Keywords:** source inversion, dipole orientation, cortical columns, cortical surface, high precision MEG

**18 Abstract**

19 Determining the anatomical source of brain activity non-invasively measured from EEG or MEG sensors  
20 is challenging. In order to simplify the source localization problem, many techniques introduce the  
21 assumption that current sources lie on the cortical surface. Another common assumption is that this  
22 current flow is orthogonal to the cortical surface, thereby approximating the orientation of cortical  
23 columns. However, it is not clear which cortical surface to use to define the current source locations,  
24 and normal vectors computed from a single cortical surface may not be the best approximation to the  
25 orientation of cortical columns. We compared three different surface location priors and five different  
26 approaches for estimating dipole vector orientation, both in simulations and visual and motor evoked  
27 MEG responses. We show that models with source locations on the white matter surface and using  
28 methods based on establishing correspondences between white matter and pial cortical surfaces  
29 dramatically outperform models with source locations on the pial or combined pial/white surfaces and  
30 which use methods based on the geometry of a single cortical surface in fitting evoked visual and motor  
31 responses. These methods can be easily implemented and adopted in most M/EEG analysis pipelines,  
32 with the potential to significantly improve source localization of evoked responses.

33

## 34 **Introduction**

35 Non-invasive measures of brain activity such as magnetoencephalography (MEG) and  
36 electroencephalography (EEG) are powerful tools for generating insights into human brain function with  
37 millisecond-scale temporal resolution. However, determining the current distribution that gives rise to  
38 the signals measured from EEG and MEG sensors is challenging (Baillet et al., 2001; Darvas et al., 2004;  
39 Fukushima et al., 2012; Haufe et al., 2011; Mattout et al., 2006). In order to simplify the source  
40 localization problem, many techniques introduce constraints to the dimensionality of source space.  
41 These constraints embody assumptions about how the brain generates the signals which we can  
42 measure from outside of the head.

43 One of these assumptions is that signals measured by M/EEG sensors are predominantly generated by  
44 large pyramidal neurons in deep cortical layers, which are arranged in parallel columns so that their  
45 cumulative activity produces a measurable extracranial signal (Baillet, 2017; Buzsáki et al., 2012;  
46 Murakami and Okada, 2006; Okada et al., 1997). Two commonly used source localization constraints  
47 based on this assumption are that the locations of source dipoles are restricted to locations on a mesh  
48 of the white matter surface as is it is closest to the deep cortical layers (Dale and Sereno, 1993; Henson  
49 et al., 2009; Hillebrand and Barnes, 2003, 2002; Mattout et al., 2007), and that the orientation of dipoles  
50 is orthogonal to this surface (Hämäläinen and Ilmoniemi, 1984, 1994; Henson et al., 2009; Hillebrand  
51 and Barnes, 2003; Lin et al., 2006; Salmelin et al., 1995), thereby approximating the orientation of  
52 cortical columns (Nunez and Srinivasan, 2006; Okada et al., 1997).

53 Using vectors orthogonal to the cortical surface may not be the best approximation to the orientation of  
54 cortical columns. Cortical folding patterns may result in curved cortical columns, and therefore their  
55 orientation with respect to the cortical surface could be different along the gray / white matter (white  
56 matter surface) and CSF / gray matter (pial surface) boundaries. Moreover, induced activity in low and  
57 high frequency bands can predominate in deep or superficial cortical layers (Bastos et al., 2015;

58 Bonaiuto et al., 2018a; Buffalo et al., 2011; Haegens et al., 2015; Maier et al., 2010; Spaak et al., 2012;  
59 van Kerkoerle et al., 2014), and therefore the white matter surface may not be the optimal source  
60 location model. In the past, however, the contribution of inaccuracies in dipole location and orientation  
61 constraints to source localization error has likely been insignificant in the face of within-session  
62 participant movement, co-registration error, and the relatively low resolution of cortical surface  
63 reconstructions. However, the recent development of techniques for high precision MEG (Bonaiuto et  
64 al., 2018b, 2018a; Meyer et al., 2017; Troebinger et al., 2014b, 2014a) allow us to compare competing  
65 current-flow orientation models in more detail.

66 Here, we set out to determine a better way to estimate the location and orientation of source dipoles  
67 based on MRI-derived cortical surfaces. We tested three different cortical surfaces for determining  
68 dipole locations: 1) white matter, 2) pial, and 3) combined white matter/pial, and five different methods  
69 for computing dipole orientations: 1) downsampled surface normals, 2) cortical patch statistics, 3)  
70 original surface normals, 4) link vectors, and 5) variational vector fields. The most commonly used  
71 method, downsampled surface normals (Dale and Sereno, 1993; Fuchs et al., 1994; Hämäläinen and  
72 Hari, 2002; Hillebrand and Barnes, 2003; Lin et al., 2006), involves downsampling (decimating) the  
73 original cortical surface, and then computing the normal vector at each vertex as the mean of the  
74 normal vectors of each surface face it is connected to. While surface decimation increases the  
75 computational tractability of source inversion, it distorts the surface faces and therefore biases the  
76 surface normal vector estimates. The cortical patch statistics method was therefore designed to  
77 compute normal vectors by averaging the individual normal vectors from vertices adjacent to the  
78 nearest vertex in the original (down-sampled) mesh (Lin et al., 2006). The original surface normals  
79 method takes advantage of the fact that the surface decimation algorithm used here maintains a  
80 correspondence between the downsampled and original surface meshes, and uses the normal vectors of  
81 the corresponding vertices from the original cortical surface. These three methods involve computation

82 of dipole orientation based on the geometry of a single cortical mesh: the white matter or pial surface.  
83 In contrast, the link vectors (Dale et al., 1999) and variational vector field (Fischl and Sereno, 2018)  
84 approaches establish correspondences between the white matter and pial surface meshes. The link  
85 vectors approach simply uses the vectors connecting each vertex on the white matter surface with the  
86 corresponding vertex on the pial surface (Dale et al., 1999). The variational vector field method  
87 constructs a field of correspondence vectors between the original white matter and pial surfaces which  
88 are constrained to be approximately normal to each cortical surface and parallel to each other (Fischl  
89 and Sereno, 2018).

90 We first compared the resulting orientation vectors from each method in terms of the angular  
91 difference at each surface vertex. We then ran simulations of single dipoles at a given orientation, and  
92 subsequently performed source reconstruction using various dipole orientations, noise levels, and co-  
93 registration error magnitudes. Finally, we compared the methods using evoked visual and motor  
94 responses in MEG data from human participants.

95

## 96 **Methods**

97 Data from eight healthy, right-handed, volunteers with normal or corrected-to-normal vision and no  
98 history of neurological or psychiatric disorders was used for our analyses (six male, aged  $28.5 \pm 8.52$   
99 years; Bonaiuto et al., 2018a; Little et al., 2018). The study protocol was in accordance with the  
100 Declaration of Helsinki, and all participants gave written informed consent which was approved by the  
101 UCL Research Ethics Committee (reference number 5833/001). All analysis code is available at  
102 [https://github.com/jbonaiuto/dipole\\_orientation](https://github.com/jbonaiuto/dipole_orientation).

103

## 104 ***MRI acquisition***

105 Prior to MEG scanning, two MRI scans were acquired with a 3T whole body MR system (Magnetom TIM  
106 Trio, Siemens Healthcare, Erlangen, Germany) using the body coil for radio-frequency (RF) transmission  
107 and a standard 32-channel RF head coil for reception. The first was a standard T1 for individual head-  
108 cast creation (Meyer et al., 2017), and the other was a high resolution, quantitative multiple parameter  
109 map (MPM; Weiskopf et al., 2013) for MEG source location.

110 The first protocol used a T1-weighted 3D spoiled fast low angle shot (FLASH) sequence with 1 mm  
111 isotropic image resolution, field-of view set to 256, 256, and 192 mm along the phase (anterior-  
112 posterior, A–P), read (head-foot, H–F), and partition (right-left, R–L) directions, respectively. The  
113 repetition time was 7.96 ms and the excitation flip angle was 12°. After each excitation, a single echo  
114 was acquired to yield a single anatomical image. A high readout bandwidth (425 Hz/pixel) was used to  
115 preserve brain morphology and no significant geometric distortions were observed in the images.  
116 Acquisition time was 3min 42s. A 12 channel head coil was used for signal reception without using either  
117 padding or headphones.

118 The second, MPM, protocol consisted of acquisition of three differentially-weighted, RF and gradient  
119 spoiled, multi-echo 3D fast low angle shot (FLASH) acquisitions and two additional calibration sequences  
120 to correct for inhomogeneities in the RF transmit field (Callaghan et al., 2015; Lutti et al., 2012, 2010),  
121 with whole-brain coverage at 800  $\mu\text{m}$  isotropic resolution.

122 The FLASH acquisitions had predominantly proton density (PD), T1 or magnetization transfer saturation  
123 (MT) weighting. The flip angle was 6° for the PD- and MT-weighted volumes and 21° for the T1 weighted  
124 acquisition. MT-weighting was achieved through the application of a Gaussian RF pulse 2 kHz off  
125 resonance with 4 ms duration and a nominal flip angle of 220° prior to each excitation. The field of view  
126 was 256 mm head-foot, 224 mm anterior-posterior (AP), and 179 mm right-left (RL). Gradient echoes  
127 were acquired with alternating readout gradient polarity at eight equidistant echo times ranging from

128 2.34 to 18.44 ms in steps of 2.30 ms using a readout bandwidth of 488 Hz/pixel. Only six echoes were  
129 acquired for the MT-weighted acquisition in order to maintain a repetition time (TR) of 25 ms for all  
130 FLASH volumes. To accelerate the data acquisition, partially parallel imaging using the GRAPPA  
131 algorithm was employed with a speed-up factor of 2 in each phase-encoded direction (AP and RL) with  
132 forty integrated reference lines.

133 To maximize the accuracy of the measurements, inhomogeneity in the transmit field was mapped by  
134 acquiring spin echoes and stimulated echoes across a range of nominal flip angles following the  
135 approach described in Lutti et al. (2010), including correcting for geometric distortions of the EPI data  
136 due to B0 field inhomogeneity. Total acquisition time for all MRI scans was less than 30 min.

137 Quantitative maps of proton density (PD), longitudinal relaxation rate ( $R1 = 1/T1$ ), MT and effective  
138 transverse relaxation rate ( $R2^* = 1/T2^*$ ) were subsequently calculated according to the procedure  
139 described in Weiskopf et al. (2013).

140

#### 141 ***FreeSurfer surface extraction***

142 FreeSurfer (v5.3.0; Fischl, 2012) was used to extract cortical surfaces from the MPMs for MEG source  
143 localization. We used a custom FreeSurfer surface reconstruction procedure to process MPM volumes,  
144 using the PD and T1 volumes as inputs (Carey et al., 2017), resulting in surface meshes representing the  
145 pial surface (adjacent to the cerebro-spinal fluid, CSF), and the white/grey matter boundary (**Figure 1**).  
146 FreeSurfer creates the pial surface by expanding the white matter surface outward to the cortex/CSF  
147 boundary. This is done by minimizing an energy functional which includes terms promoting surface  
148 smoothness and regularity as well as an intensity-based term designed to determine the cortex/CSF  
149 boundary based on local volume intensity contrast (Dale et al., 1999). Because this process involves  
150 moving the vertices of the white matter surface based on the gradient of the energy functional, the



151 result is a one-to-one correspondence between white matter and pial surface vertices. We used a  
152 custom routine to downsample each of these surfaces by a factor of 10 while maintaining this  
153 correspondence. This involved using MATLAB's `reducepatch` function to remove vertices from, and re-  
154 tessellate the pial surface, and then removing the same vertices from the white matter surface and  
155 copying the edge structure from the pial surface. This yielded two meshes of the same size (same  
156 number of vertices and edges), comprising about 30,000 vertices each ( $M = 30,094.75$ ,  $SD = 2,665.45$   
157 over participants).

158

### 159 ***Dipole orientation computation methods***

160 The downsampled surface normal method computes, at each vertex of the decimated mesh, the  
161 average of the normal vectors of each adjacent face (**Figure 1**). This method was implemented using the  
162 `spm_mesh_normals` function in SPM12. The cortical patch statistics method computes, at each vertex of  
163 the decimated mesh, the average surface normal vector over all vertices in the original, non-decimated  
164 mesh which are adjacent to the corresponding original mesh vertex (**Figure 1**). The original surface  
165 normal method is implemented in the same way as the downsampled surface normals method, but is  
166 applied to the original, non-decimated mesh (**Figure 1**). Because our decimation procedure only  
167 removed vertices from the original surface, the resulting vectors can then be mapped onto the vertices  
168 of the decimated mesh used for source localization. The link vectors method takes advantage of the fact  
169 that our decimation routine maintains the correspondence between white matter and pial surface  
170 vertices, and for each vertex on the pial surface, uses the vector linking it to the corresponding vertex on  
171 the white matter surface ( $\mathbf{v}_i = \mathbf{w}_i - \mathbf{p}_i$ , for the  $i^{\text{th}}$  white matter vertex,  $\mathbf{w}_i$ , and pial vertex  $\mathbf{p}_i$ ; **Figure 1**). The  
172 variational vector field method constructs a vector field linking the white matter and pial surfaces, by  
173 using gradient descent to minimize an energy functional that encourages vectors to approximate surface

174 normals and to be parallel to each other (Fischl and Sereno, 2018) (**Figure 1**). The angular difference  
 175 between any two vectors,  $\mathbf{v}_1$  and  $\mathbf{v}_2$ , was computed using the formula:  $\text{atan2}(\|\mathbf{v}_1 \times \mathbf{v}_2\|, \mathbf{v}_1 \cdot \mathbf{v}_2)$ .

176 Vectors obtained from each method were used to construct the lead field matrix of the forward model  
 177 used for source inversion of the simulated or experimental data. The models constructed using each  
 178 method were compared to each other based on relative Bayesian model evidence, as approximated by  
 179 differences in free energy:

$$180 \quad \Delta F_{i,j} = F_i - F_j$$

181 where  $F_i$  and  $F_j$  are the free energy values of models  $i$  and  $j$ , respectively. Free energy is a parametric  
 182 metric rewards fit accuracy and penalizes model complexity (Bonaiuto et al., 2018b; Friston et al., 2008,  
 183 2007; Henson et al., 2009; López et al., 2014; Wipf and Nagarajan, 2009):

$$184 \quad F_i = \text{Accuracy}(i) - \text{Complexity}(i)$$

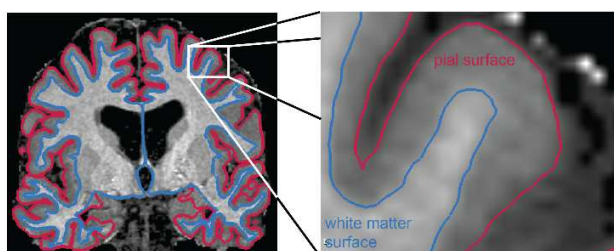
185 The first term is the log model evidence: the log of the probability of the data, given the model and  
 186 parameters, and the second term is the Kullback-Liebler divergence between the true posterior density  
 187 and an approximate posterior density. Because the second term is always positive, free energy provides  
 188 a lower bound on the model evidence (Penny et al., 2010).

189 The best overall dipole orientation method and source space surface model was determined using  
 190 random effects family level Bayesian inference (Penny et al., 2010) as implemented by the  
 191 `spm_compare_families` method in SPM12. This method groups models based on visual ERF 1 and 2 and  
 192 the motor ERF in all participants into ‘families’, and then combines the evidence of models from the  
 193 same family and computes the exceedance probability for each family. The exceedance probability  
 194 corresponds to the belief that a particular model family is more likely than the other model families  
 195 tested, given the data from all participants. We first grouped models into families based on dipole  
 196 orientation method / source space surface model combinations (e.g. downsampled surface normals /

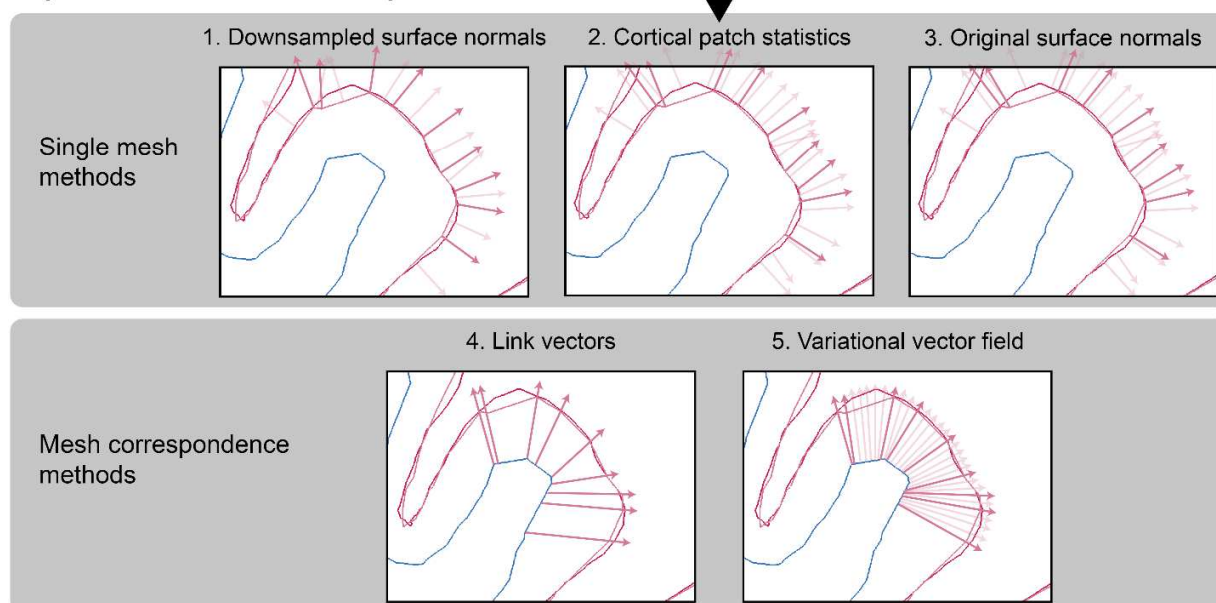
197 pial surface) to determine the best combination over all ERFs and participants. We then grouped models  
 198 based on dipole orientation method, and finally based on source space surface model.

199

## Segmentation and surface extraction



## Dipole orientation computation



200

201 **Figure 1. Dipole orientation models.**

202 *Pial and white matter surfaces are extracted from proton density and T1 weighted quantitative maps obtained from a multi-*  
 203 *parameter mapping MRI protocol. Dipole orientation vectors are computed from these surfaces using five different methods.*  
 204 *The downsampled surface normal and original surface normal methods compute vectors at each vertex (dark red) as the mean*  
 205 *of the normal vectors of the surface faces they are connected to (light red). The cortical patch statistics method computes the*  
 206 *mean of the normal vertices adjacent to the corresponding vertices in the original mesh. The link vectors method computes*  
 207 *vectors which link corresponding vertices on the white matter and pial surfaces. The variational vector field method constructs a*  
 208 *field of vectors which are approximately parallel to each other and orthogonal to the pial surface (shown in light red for the*  
 209 *original surfaces and dark red for the subset of vertices in the downsampled surfaces).*

210

211 **Simulations**

212 All simulations were based on a single dataset acquired from one human participant. This dataset was  
213 only used to determine the sensor layout, sampling rate (1200 Hz, downsampled to 250 Hz), number of  
214 trials (515), and number of samples (251) for the simulations. All simulations and analyses were  
215 implemented using the SPM12 software package (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>).

216 In each simulation, we specified spatially distributed source activity centered at a single vertex on the  
217 pial surface. We simulated a Gaussian activity time course in this vertex, centered within the epoch, with  
218 a width of 25ms and a magnitude of 10nAm. We then spatially smoothed this simulated dipole time  
219 course with a Gaussian kernel (FWHM=5mm), to obtain a patch of spatially distributed activity. Within  
220 this patch, the orientation of each vertex differed, but was specified by the same rule using the link  
221 vectors method. We then used a single shell forward model (Nolte, 2003) to generate a synthetic  
222 dataset from the simulated source activity. We simulated sources at 100 random vertices on the pial  
223 surface, and ran two sets of simulations: one varying the level of noise in the simulated data and the  
224 other varying the magnitude of co-registration error.

225 Typical per-trial SNR levels for MEG data range from -40 to -20 dB (Goldenholz et al., 2009), and  
226 therefore Gaussian white noise was added to the simulated data and scaled in order to yield per-trial  
227 amplitude SNR levels (averaged over all sensors) of -50, -40, -30, -20, -10, or 0 dB to generate synthetic  
228 datasets across a range of realistic SNRs. Source reconstruction was performed using 10 different  
229 models. The reference model used the original link vectors as dipole orientation priors, and the  
230 remaining 9 models used vectors with angular differences from the original link vectors ranging from 7  
231 to 63 degrees (in increments of 7 degrees). The orientation of the 9 additional vectors was determined  
232 by taking random points on the edge of a cone defined by the reference vector and the angular distance.  
233 In these simulations, the co-registration error was 0mm. Within each SNR level, the free energy metric  
234 was compared between each model and the reference model.

235 Within-session head movement and between-session co-registration error commonly combine to  
236 introduce a typical magnitude of ~5mm (or more) of uncertainty concerning the relative location of the  
237 brain and the MEG sensors in traditional MEG recordings (Adjamian et al., 2004; Gross et al., 2013; Ross  
238 et al., 2011; Singh et al., 1997; Stolk et al., 2013; Whalen et al., 2008). To simulate between-session co-  
239 registration error, we therefore introduced a linear transformation of the fiducial coil locations in  
240 random directions (0mm translation - 0° rotation, 2mm - 2°, 4mm - 4°, 6mm - 6°, 8mm - 8°, or 10mm -  
241 10°) prior to source inversion. As in the SNR simulations, source reconstruction was performed using a  
242 reference model with the original link vectors as orientation priors, and 9 models using vectors rotated  
243 in random directions with angular differences from the original vectors from 7 to 63 degrees. In these  
244 simulations, the per-trial amplitude SNR was set to 0dB. Within each level of co-registration error, we  
245 compared the free energy between each model and the reference model.

246

#### 247 ***Head-cast construction***

248 From an MRI-extracted image of the scalp, a head-cast that fit between the participant's scalp and the  
249 MEG dewar was constructed (Bonaiuto et al., 2018a; Meyer et al., 2017; Troebinger et al., 2014b). Scalp  
250 surfaces were first extracted from the T1-weighted MRI scans acquired in the first MRI protocol using  
251 SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). This tessellated surface, along with 3D models of fiducial  
252 coils placed on the nasion and the left and right pre-auricular points, was used to create a virtual 3D  
253 model, which was then placed inside a virtual version of the scanner dewar in order to minimize the  
254 distance to the sensors while ensuring that the participant's vision was not obstructed. The model  
255 (including spacing elements and fiducial coil protrusions) was printed using a Zcorp 3D printer (Zprinter  
256 510). The 3D printed model was then placed inside a replica of the MEG dewar and polyurethane foam  
257 was poured in between the surfaces to create the participant-specific head-cast. The protrusions in the  
258 3D model for fiducial coils therefore become indentations in the foam head-cast, into which the fiducial

259 coils can be placed scanning. The locations of anatomical landmarks used for co-registration are thus  
260 unchanged over repeated scans, allowing combination of data from multiple sessions (Bonaiuto et al.,  
261 2018a; Meyer et al., 2017).

262

### 263 ***Behavioral task***

264 Participants completed a visually cued action decision making task in which they responded to visual  
265 instruction cue projected on a screen by pressing one of two buttons using the index and middle finger  
266 of their right hand (Bonaiuto et al., 2018a). After a baseline period of fixation, a random dot  
267 kinematogram (RDK) was displayed for 2s with coherent motion either to the left or to the right.  
268 Following a delay period, an instruction cue (an arrow pointing either to the left or the right), prompted  
269 participants to press either the left or right button. The level of motion coherence in the RDK and the  
270 congruence between the RDK motion direction and instruction cue varied from trial to trial, but for the  
271 purposes of the present study, we analyzed the main effect of visual stimulus onset and button press  
272 responses. For a full description of the paradigm and task structure, see Bonaiuto et al. (2018a).

273 Each block contained 180 trials in total. Participants completed three blocks per session, and 1–5  
274 sessions on different days, resulting in 540–2700 trials per participant ( $M = 1822.5$ ,  $SD = 813.21$ ). The  
275 task was implemented in MATLAB (The MathWorks, Inc., Natick, MA) using the Cogent 2000 toolbox  
276 (<http://www.vislab.ucl.ac.uk/cogent.php>).

277

### 278 ***MEG acquisition and preprocessing***

279 MEG data were acquired using a 275-channel Canadian Thin Films (CTF) MEG system with  
280 superconducting quantum interference device (SQUID)-based axial gradiometers (VSM MedTech,  
281 Vancouver, Canada) in a magnetically shielded room. A projector was used to display visual stimuli on a

282 screen (~50 cm from the participant), and a button box was used for participant responses. The data  
283 collected were digitized continuously at a sampling rate of 1200 Hz. MEG data preprocessing and  
284 analyses were performed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) using MATLAB R2014a. The  
285 data were filtered (5th order Butterworth bandpass filter: 2–100 Hz, Notch filter: 50 Hz) and  
286 downsampled to 250Hz. Eye blink artifacts were removed using multiple source eye correction (Berg and  
287 Scherg, 1994). Trials were then epoched from 1s before RDK onset to 1.5s after instruction cue onset for  
288 analysis of visual responses, and from 2s before the participant's response to 2s after for analysis of  
289 movement-evoked responses. Blocks within each session were merged, and trials whose variance  
290 exceeded 2.5 standard deviations from the mean were excluded from analysis. The epoched data were  
291 then averaged over trials using robust averaging, a form of general linear modeling (Wager et al., 2005)  
292 used to reduce the influence of outliers on the mean by iteratively computing a weighting factor for  
293 each sample according to how far it is from the mean. Preprocessing code is available at  
294 <http://github.com/jbonaiuto/meg-laminar>.

295

### 296 ***Source reconstruction***

297 Source inversion was performed using the empirical Bayesian beamformer algorithm (EBB; Belardinelli  
298 et al., 2012; López et al., 2014) as implemented in SPM12. The source inversion was applied to a 100ms  
299 time window, centered on the event of interest (the peak of the simulated signal, 100ms following the  
300 onset of visual stimuli, or the button press response). These data were projected into 274 orthogonal  
301 spatial (lead field) modes and 4 temporal modes. Singular value decomposition (SVD) was used to  
302 reduce the sensor data to 274 orthogonal spatial (lead field) modes, each with 4 temporal modes  
303 (weighting the dominant modes of temporal variation across the window). For uninformative priors, the  
304 maximum-likelihood solution to the inverse problem is:

305 
$$\hat{J} = QL^T(Q_\epsilon + LQL^T)^{-1}Y$$

306 where  $\hat{J}$  is the estimated current density across the source space,  $Y$  is the SVD-reduced measured data,  $L$   
 307 is the lead field matrix that can be computed from the sensor and volume conductor geometry.  $Q_\epsilon$  is the  
 308 sensor covariance and  $Q$  is the prior estimate of source covariance. We assumed the sensor level  
 309 covariance ( $Q_\epsilon$ ) to be an identity matrix (see discussion). Most inversion algorithms can be differentiated  
 310 by the form of  $Q$  (Friston et al., 2008; López et al., 2014). EBB uses a beamformer prior to estimate the  
 311 structure of  $Q$  (Belardinelli et al., 2012; López et al., 2014) based on the sensor-level data:

312 
$$Q(i) = \frac{1}{L_i^T L_i} (L_i^T (YY^T)^{-1} L_i + \lambda I)^{-1}$$

313 where each element of the diagonal  $Q(i)$  corresponds to a source location  $i$ . The lead field of each source  
 314 location is  $L_i$ ,  $^T$  denotes the transpose operator,  $I$  is an identity matrix, and  $\lambda$  is a regularization constant  
 315 (set to 0). The prior estimates of  $Q_\epsilon$  and  $Q$  are then re-scaled or optimally mixed using an expectation  
 316 maximization scheme (Friston et al., 2008) to give an estimate of  $J$  that maximizes model evidence. All  
 317 inversions used a spatial coherence prior (Friston et al., 2008) with a FWHM of 5 mm. We used the  
 318 Nolte single shell head model (Nolte, 2003).

319 For MEG source inversion, the accuracy term of the free energy equation is defined as

320 
$$\text{Accuracy}(i) = \frac{N_c}{2} \text{trace}(C_Y C_i^{-1}) - \frac{N_c}{2} \log|C_i| - \frac{N_c N_t}{2} \log(2\pi)$$

321 where  $N_c$  is the number of channels,  $N_t$  is the number of samples,  $C_Y = \frac{1}{N_c} YY^T$  is the data-based  
 322 sampled covariance,  $C_i = Q_\epsilon + L_i Q L_i^T N_t$  is the model-based sample covariance, and  $|\cdot|$  is the matrix  
 323 determinant operator.



324 For the EBB algorithm, the complexity term of the free energy equation is dependent on  
 325 hyperparameters,  $\lambda$ , that control the trade-off between sensor noise  $Q_\epsilon = \lambda_1 I_{N_c}$ , and the beamforming  
 326 prior  $Q = \lambda_2 \Gamma$ , where  $\Gamma$  is the beamforming prior:

$$327 \quad \text{Complexity}(i) = \frac{1}{2} (\hat{\lambda}_i - v)^T \Pi (\hat{\lambda}_i - v) + \frac{1}{2} \log |\Sigma_{\lambda_i} \Pi|$$

328 The prior and posterior distributions of  $\lambda$ ,  $q(\lambda_i)$  and  $p(\lambda_i)$  are assumed to be Gaussian:

$$329 \quad q(\lambda_i) = N(\lambda; v, \Pi^{-1})$$

$$330 \quad p(\lambda_i) = N(\hat{\lambda}_i, \Sigma_{\lambda_i})$$

331 where  $\hat{\lambda}_i$  and  $\Sigma_{\lambda_i}$  are the posterior mean and covariance of the hyperparameters for model  $i$ . We used  
 332 non-informative mean and precision ( $v$  and  $\Pi$ ) implemented as identity matrices scaled close to zero  
 333 mean and low precision, as implemented by default in SPM.

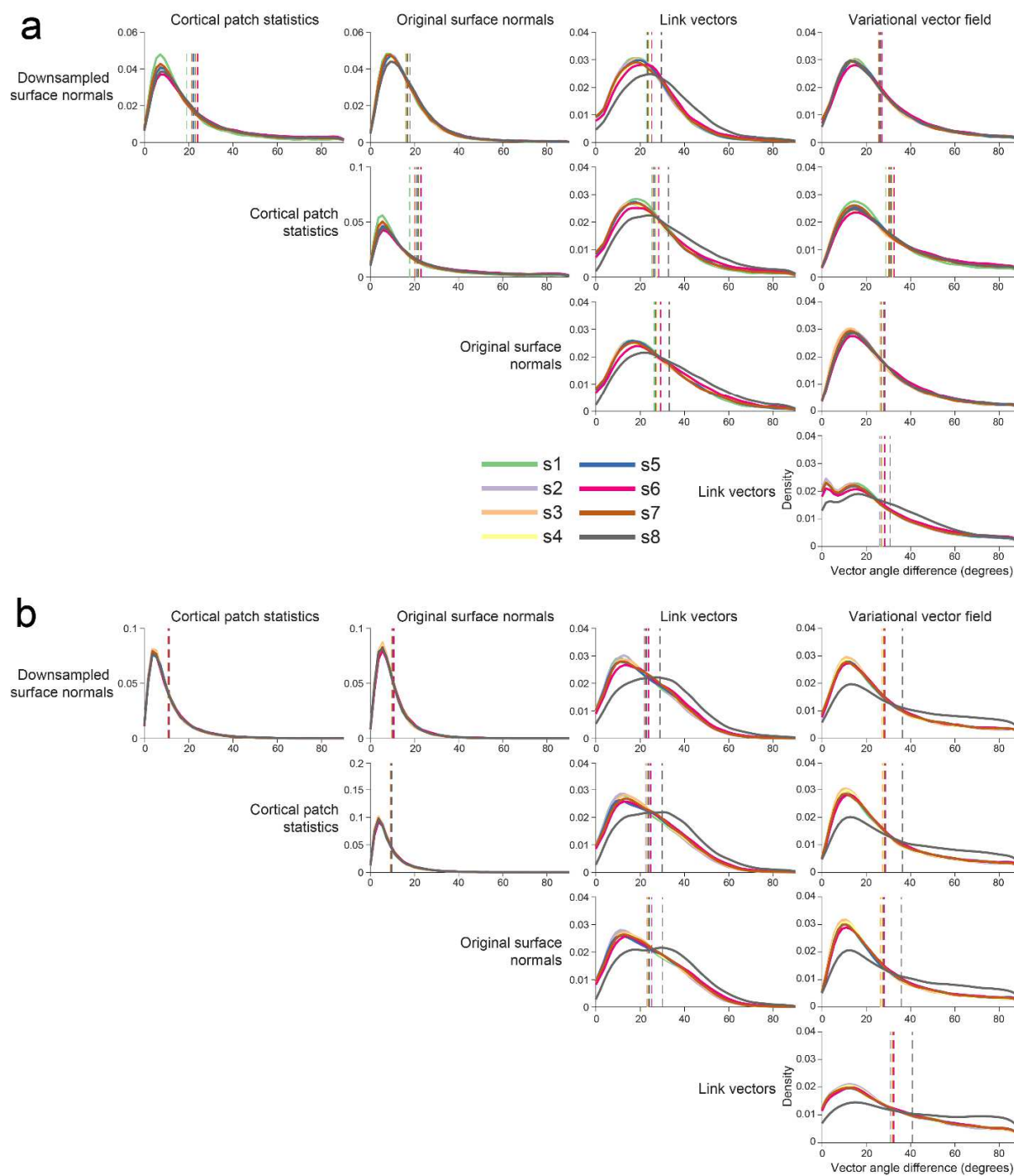
334

## 335 **Results**

### 336 ***Different methods for estimating vector orientation yield substantial variation in dipole orientation***

337 We first compared the dipole orientation vectors generated by each of our five methods in terms of the  
 338 angular difference between vectors at the same vertex on the pial and white matter surfaces,  
 339 respectively (**Figure 2**). The three methods that utilize only one surface, (downsampled surface normals,  
 340 cortical patch statistics, original surface normals) generated vectors which were the most similar to each  
 341 other on both the pial (downsampled surface normals – cortical patch statistics individual subject mean  
 342 angular difference: 19.16-23.04°; over subjects: M=22.30°, SD=1.51°; downsampled surface normals –  
 343 original surface normals: 16.00-17.95°; over subjects: M=16.94°, SD=0.67°; cortical patch statistics –  
 344 original surface normals: 17.80-22.89°; over subjects: M=21.01°, SD=1.55°) and white matter surfaces  
 345 (downsampled surface normals – cortical patch statistics individual subject mean angular difference:

346 10.65-11.35°; over subjects:  $M=10.99^\circ$ ,  $SD=0.27^\circ$ ; downsampled surface normals – original surface  
347 normals: 9.64-10.57°; over subjects:  $M=10.10^\circ$ ,  $SD=0.32^\circ$ ; cortical patch statistics – original surface  
348 normals: 8.93-9.76°; over subjects:  $M=9.34^\circ$ ,  $SD=0.31^\circ$ ). Each single- and multi-surface method  
349 generated vectors with mean angular differences from each other of at least 20°, for both the pial  
350 surface (downsampled surface normals – link vectors: 22.94-29.56°,  $M=24.51^\circ$ ,  $SD=2.15^\circ$ ; downsampled  
351 surface normals – variational vector field: 25.52-27.13°,  $M=26.05^\circ$ ,  $SD=0.55^\circ$ ; cortical patch statistics –  
352 link vectors: 25.26-32.76°,  $M=27.42^\circ$ ,  $SD=2.06^\circ$ ; cortical patch statistics – variational vector field: 28.80-  
353 32.55°,  $M=30.91^\circ$ ,  $SD=1.11^\circ$ ; original surface normals – link vectors: 26.77-33.12°,  $M=28.44^\circ$ ,  $SD=2.06^\circ$ ;  
354 original surface normals – variational vector field: 26.18-28.43°,  $M=27.06^\circ$ ,  $SD=0.75^\circ$ ) and the white  
355 matter surface (downsampled surface normals – link vectors: 21.81-29.03°,  $M=23.46^\circ$ ,  $SD=2.33^\circ$ ;  
356 downsampled surface normals – variational vector field: 27.08-36.26°,  $M=28.78^\circ$ ,  $SD=3.06^\circ$ ; cortical  
357 patch statistics – link vectors: 22.64-24.82°,  $M=24.48^\circ$ ,  $SD=2.34^\circ$ ; cortical patch statistics – variational  
358 vector field: 27.31-36.34°,  $M=29.04^\circ$ ,  $SD=3.00^\circ$ ; original surface normals – link vectors: 23.38-30.09°,  
359  $M=25.00^\circ$ ,  $SD=2.15^\circ$ ; original surface normals – variational vector field: 26.43-35.69°,  $M=28.31^\circ$ ,  
360  $SD=3.08^\circ$ ). The two multi-surface methods, link vectors and variational vector field, generated vectors  
361 with some of the largest mean angular differences of all method pairs on each surface (pial surface:  
362 67.41-30.74°,  $M=27.71^\circ$ ,  $SD=1.40^\circ$ ; white matter surface: 31.33-40.74°,  $M=33.31^\circ$ ,  $SD=3.04^\circ$ ). These  
363 results were comparable when using surfaces derived from more commonly used 1mm<sup>3</sup> T1 scans  
364 instead of 800μm<sup>3</sup> MPMs (**Figure S1**). Therefore, rather than being close approximations to each other,  
365 each method generates substantially different dipole orientation vectors, even within the multi-surface  
366 class of methods.

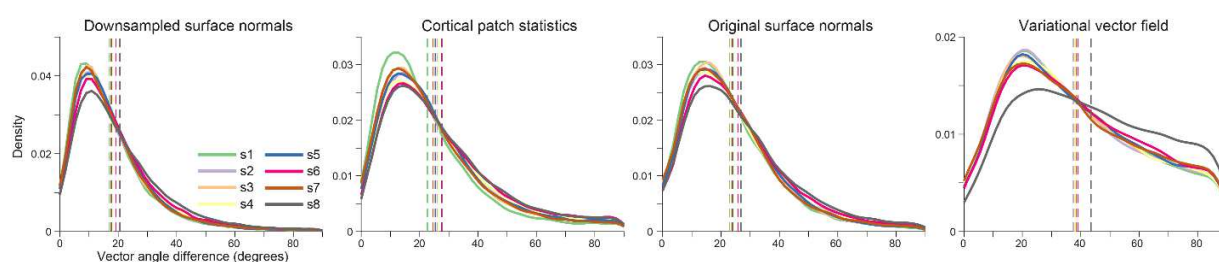


367

368 **Figure 2. Substantial discrepancy in dipole orientations across methods.**369 *Distribution of angular difference between dipole orientations on the pial surface (a) and white matter surface (b), generated*370 *using each method for each participant. Vertical dashed lines show the mean angular difference for each participant.*

371

372 We next compared dipole orientation vectors generated by each method between the pial and white  
 373 matter surfaces derived from the  $800\mu\text{m}^3$  MPM volumes (**Figure 3**) and  $1\text{mm}^3$  T1 volumes (**Figure S2**).  
 374 Because the link vectors method generates vectors that connect corresponding vertices on the pial and  
 375 white matter surfaces, the resulting dipole orientations on each surface are equivalent (i.e. the link  
 376 vector from a particular vertex on the pial surface points in exactly the opposite direction as the link  
 377 vector from the corresponding white matter surface vertex). All three single-surface methods generated  
 378 vectors with the lowest average angular difference between pial and white matter surfaces created  
 379 using either the  $800\mu\text{m}^3$  MPM volumes (downsampled surface normals: individual subject mean angular  
 380 difference= $16.88\text{--}20.52^\circ$ , over subjects  $M=18.23^\circ$ ,  $SD=1.13^\circ$ ; cortical patch statistics:  $22.66\text{--}27.81^\circ$ ,  
 381  $M=25.70^\circ$ ,  $SD=1.67^\circ$ ; original surface normals:  $22.90\text{--}26.81^\circ$ ,  $M=24.46^\circ$ ,  $SD=1.26^\circ$ ) or the  $1\text{mm}^3$  T1  
 382 volumes (downsampled surface normals:  $17.89\text{--}19.49^\circ$ ,  $M=18.66^\circ$ ,  $SD=0.56^\circ$ ; cortical patch statistics:  
 383  $25.10\text{--}27.23^\circ$ ,  $M=26.23^\circ$ ,  $SD=0.70^\circ$ ; original surface normals:  $24.10\text{--}28.80^\circ$ ,  $M=25.45^\circ$ ,  $SD=1.46^\circ$ ). The  
 384 variational vector field method generated dipole orientation vectors that differed the most between the  
 385 pial and white matter surface (MPM:  $37.47\text{--}43.54^\circ$ ,  $M=38.80^\circ$ ,  $SD=1.99^\circ$ ; T1:  $37.07\text{--}40.28^\circ$ ,  $M=39.10^\circ$ ,  
 386  $SD=1.00^\circ$ ). Aside from the link vectors method, there is therefore at least as much variation in dipole  
 387 orientations between the pial and white matter surfaces within a method as there is between methods  
 388 for one surface.

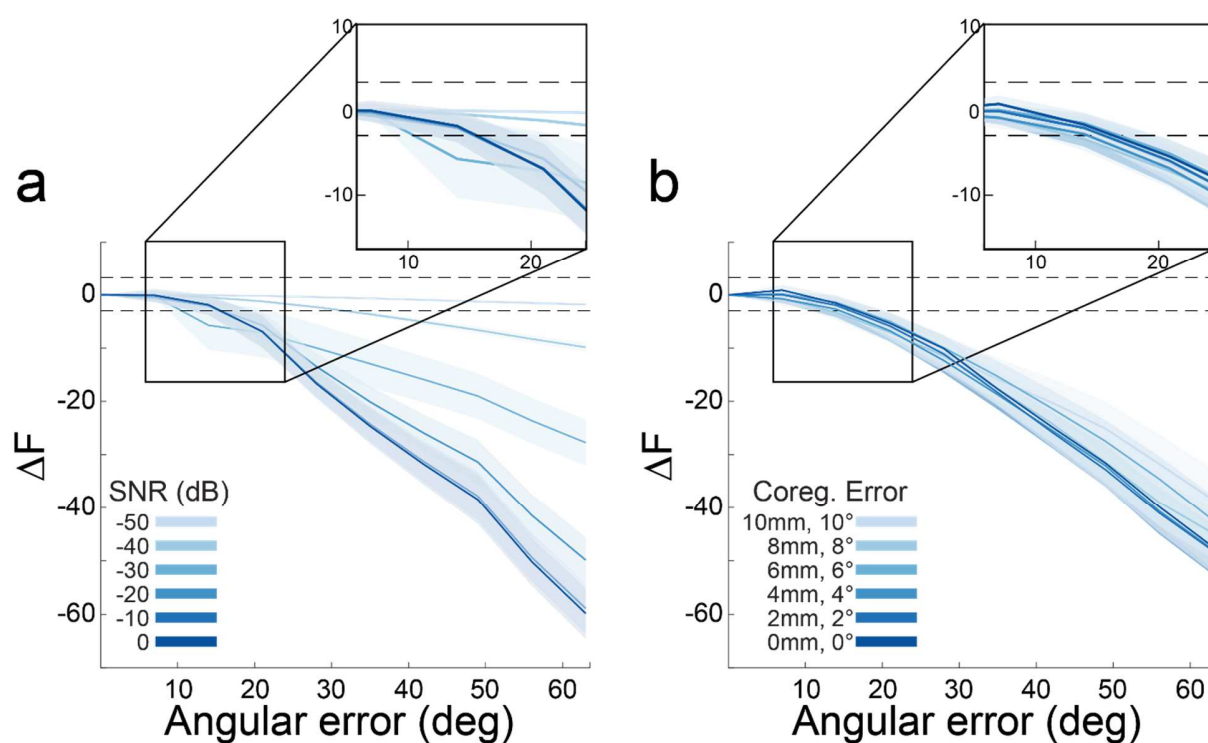


389 **Figure 3. Substantial discrepancy in dipole orientations between pial and white matter surfaces.** Distribution of angular  
 390 difference between dipole orientations at corresponding vertices on the pial and white matter surfaces, generated using the  $800$   
 391  $\mu\text{m}^3$  MPM volumes. The link vectors method is not shown because this method generates identical dipole orientations for the  
 392 pial and white matter surfaces. Each solid line shows the distribution for a single participant. Vertical dashed lines show the  
 393 mean angular difference for each participant.  
 394

395

396 ***With high precision MEG data, getting the orientation right matters***

397 Having established that each method yields substantially different orientation vectors, we next sought  
 398 to determine the minimum angular difference between dipole orientations distinguishable by source  
 399 inversion model comparison, and how this is affected by typical levels of SNR and co-registration error.  
 400 We therefore simulated dipoles at 100 random source locations on the pial surface and created  
 401 synthetic datasets with varying SNR and co-registration error levels. We then performed source  
 402 inversion on the synthetic datasets, using a reference model in which the dipole orientations exactly  
 403 match those of the simulated dipole, and 9 other models in which the dipole orientations were rotated  
 404 with respect to simulated dipole orientation. We then compared each of these models to the reference  
 405 model in terms of the relative free energy, using a significance threshold of  $\pm 3$  for the free energy  
 406 difference (indicating that one model is approximately twenty times more likely than the other).



407

408 ***Figure 4. With high precision MEG data, model evidence decreases with dipole orientation error.***

409 *a Each line shows the change in model evidence ( $\Delta F$ ) as the orientation of the dipole used for inversion is rotated away from the*  
 410 *true orientation at different SNR levels (co-registration error=0mm). The shaded regions represent the standard error of  $\Delta F$  over*

411 *all 100 simulations at each angular error value tested. The lower dotted line (at  $\Delta F=-3$ ) show the point at which the imperfect*  
412 *model is 20 times less likely than the true model. The differences between models become more apparent at higher SNR.*  
413 ***b** As in **a**, for different magnitudes of co-registration error (SNR=0dB). Co-registration error has a smaller impact than SNR on*  
414 *discriminating between models with different dipole orientations.*

415

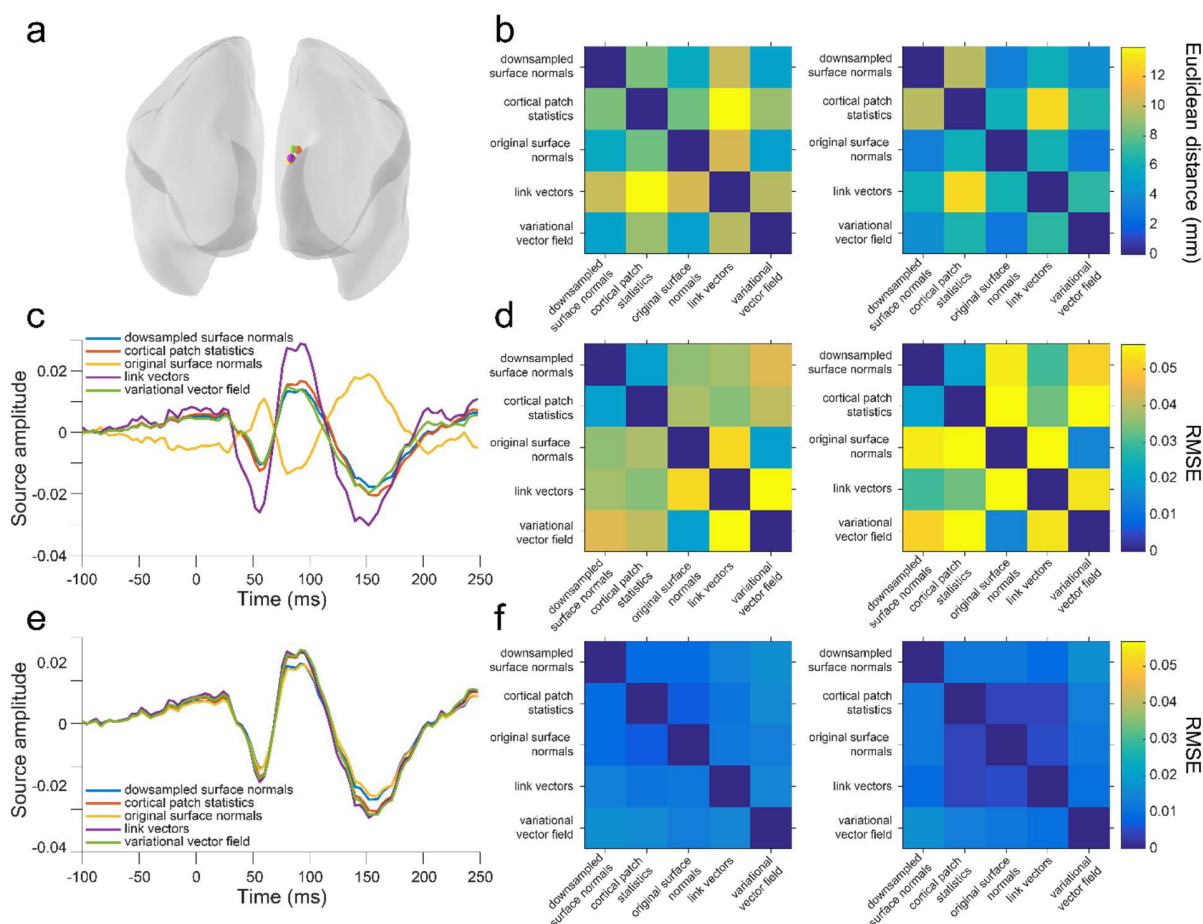
416 At lower SNR levels (-50dB), each model was indistinguishable from the reference model (magnitude of  
417 relative free energy less than 3). However, as SNR increased, models with an angular error as low as 15  
418 degrees relative to the reference model started to become differentiable (i.e., a relative free energy  
419 difference of  $>3$ ; **Figure 4a**). Relative model evidence was less dependent on co-registration error, and at  
420 all levels tested models with an angular error of at least 15 degrees could be differentiated from the  
421 reference model (**Figure 4b**). This angular error is well within the range of the angular differences  
422 between vectors generated by each of the methods considered here (**Figure 2**). In other words, given  
423 sufficient SNR and co-registration accuracy, one should be able to determine the best method to use  
424 with human data based on source inversion model comparison.

425

#### 426 ***Comparing surface models with empirical head-cast data***

427 We next compared orientation models based on three different evoked responses from human  
428 participants. We performed source inversion, and compared the resulting model fits in terms of relative  
429 free energy compared to that of the downsampled surface normal model (the current most commonly  
430 used method). This was repeated using source space models restricted to the pial surface, white matter  
431 surface, and combined pial – white matter surface (Bonaiuto et al., 2018a, 2018b). In this case the  
432 combined pial-white model had double the number of sources and these sources could be arranged  
433 with identical orientations on each surface (link vectors); or different orientations (cortical patch  
434 statistics, downsampled surface normals, original surface normals, and variational vector field).

435 The evoked response fields (ERFs) were the visually-evoked response to the RDK (visual ERF 1) and  
436 instruction cue (visual ERF 2), and the motor-evoked response during the button press (motor ERF).  
437 When running the source inversion over the full time course of each ERF, each orientation model  
438 yielded slightly different peak cortical locations (**Figure 5a, b**), with the original surface normals and  
439 variational vector field methods giving the closest peak coordinates ( $M=4.88\text{mm}$ ,  $SD=2.93\text{mm}$ ), and the  
440 cortical patch statistics and link vectors methods yielding coordinates furthest away from each other  
441 ( $M=13.96\text{mm}$ ,  $SD=12.76\text{mm}$ ). At each peak location identified by the downsampled surface normals  
442 method, the source space ERFs given by the downsampled surface normals, cortical patch statistics, and  
443 variational vector field methods, respectively, were most similar to each other, whilst the link vectors  
444 methods yielded an ERF with a larger amplitude, and the original surface normals method yielded an  
445 ERF with inverted polarity ( $RMSE<0.1$ ; **Figure 5c, d**). However, at the peak coordinate identified by each  
446 method the ERFs were very similar ( $RMSE<0.05$ ; **Figure 5e, f**).



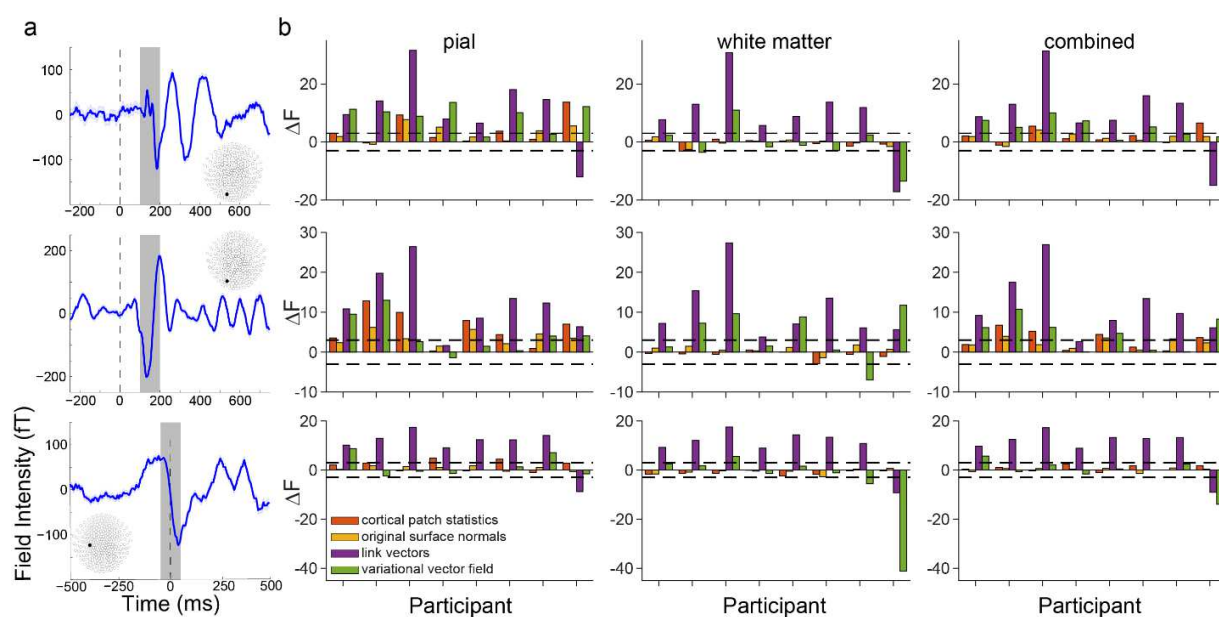
447  
 448 **Figure 5: Variation in source localization across methods.**  
 449 *a* Peak source locations on the pial surface for visual ERF1, for each dipole orientation method, in a single subject.  
 450 *b* Mean (left) and standard deviation (right) of the Euclidean distance between peak source locations for each method, using the  
 451 pial surface, over subjects and ERFs.  
 452 *c* Time course of source activity for visual ERF1 for the different methods, at the peak pial source location identified using the  
 453 downsampled surface normals method, for a single subject.  
 454 *d* Mean (left) and standard deviation (right) of the RMSE between source activity time courses at the peak source location  
 455 identified using the downsampled surface normals method, for each method, using the pial surface, over subjects and ERFs.  
 456 *e* Time course of source activity for visual ERF1 at the peak pial source location identified from each method, for a single subject.  
 457 *f* Mean (left) and standard deviation (right) of the RMSE between source activity time courses at the peak source location  
 458 identified using each method with the pial surface, over subjects and ERFs.

459 We then compared each method in terms of model fit. The link vectors method achieved a significantly  
 460 better model fit than the downsampled surface normal method in 7/8 subjects for visual ERF 1 and 2  
 461 and the motor ERF using the pial surface, 7/8 subjects for visual ERF 1 and the motor ERF and 8/8  
 462 subjects for visual ERF 2 using the white matter surface, and 7/8 subjects for visual ERF 1 and 2 and the  
 463 motor ERF using the two-layer surface (**Figure 6b**). The variational vector field method had significantly  
 464 better model fit than the downsampled surface normal method in 6/8 subjects for visual ERF 1 and 4/8



465 subjects for visual ERF2, but only 2/8 subjects for the motor ERF using the pial surface, 1/8 subjects for  
466 visual ERF 1 and the motor ERF and 4/8 subjects for visual ERF 2 using the white matter surface, and 5/8  
467 subjects for visual ERF 1 and 2 and 1/8 subjects for the motor ERF using the two-layer surface. The  
468 original surface normal method was most similar to the downsampled surface normal method, only  
469 being significantly better in 4/8 subjects for visual ERF1, 5/8 subjects for visual ERF2, and 0/8 subjects  
470 for the motor ERF using the pial surface, 0/8 subjects for visual ERF 1 and 2 and the motor ERF using the  
471 white matter surface, and 1/8 subjects for visual ERF 1, 3/8 subjects for visual ERF2, and 0/8 subjects for  
472 the motor ERF using the two-layer surface. The cortical patch statistics method was significantly better  
473 than the downsampled surface normals method in 3/8 subjects for visual ERF 1, 6/8 subjects for visual  
474 ERF 2, and 2/8 subjects for the motor ERF using the pial surface, 0/8 subjects for visual ERF 1 and 2 and  
475 the motor ERF using the white matter surface, and 2/8 subjects for visual ERF 1, 4/8 subjects for visual  
476 ERF 2, and 0/8 subjects for the motor ERF.

477 While the cortical patch statistics and original surface normal methods are an improvement on the  
478 widely used downsampled surface normal method, multi-surface methods such as link vectors and  
479 variational vector fields achieve better model fits overall, using either single- or two-layer cortical  
480 surface models (**Figure 6b**). These results were comparable when using surfaces derived from more  
481 commonly used 1mm<sup>3</sup> T1 scans instead of 800μm<sup>3</sup> MPMs, with the exception of the variational vector  
482 field method, which performed significantly worse than the downsampled surface normal method in 6/8  
483 subjects for the motor ERF using the pial surface (**Figure S3**).



484

485 **Figure 6. Surface correspondence-based methods yield the best model fit.**

486 **a** Trial-averaged event-related fields (ERFs) aligned to the onset of visual stimulus 1 (the random dot kinematogram; top), visual  
 487 stimulus 2 (the instruction cue; middle), and to the participant's response (button press; bottom). Data shown are for a single  
 488 representative participant. The inlays show the MEG sensor layout with filled circles denoting the sensor from which the ERFs  
 489 are recorded. Each shaded region represents the time window over which source inversion was performed.

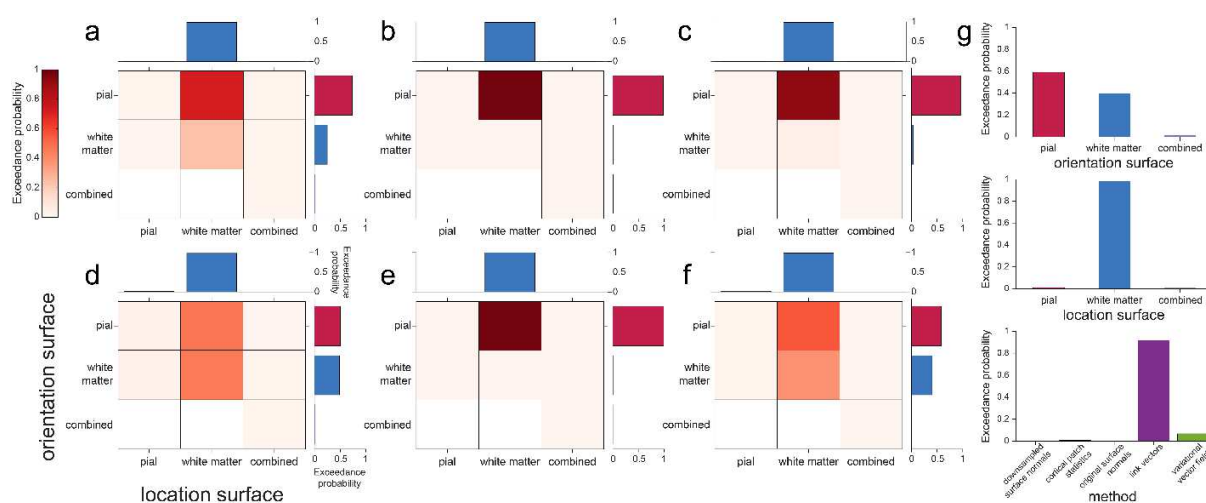
490 **b** Change in free energy (relative to the downsampled surface normals model) for each method tested for each participant for  
 491 visual ERF 1 (top), visual ERF 2 (middle), and the motor ERF (bottom) using vectors derived from  $800\mu\text{m}^3$  MPM volumes and  
 492 source space models based on the pial (left), white matter (center), and combined pial / white matter surfaces (right).

493

494 **Interaction between orientation and source space models**

495 We next sought to establish how the orientation models interacted with the different possible choices  
 496 of source space, specifically the cortical surface used to define source locations and the surface used to  
 497 compute dipole orientations. We fit the empirical evoked response data, using source space location  
 498 models based on the white matter, pial, or combined white matter/pial surfaces, and for each  
 499 orientation model using the white matter, pial, or combined white matter/pial surfaces (with the  
 500 exception of the combined surface source space orientation model which can only be used with the  
 501 combined surface source space location model).

502



503  
 504 **Figure 7. Source inversion using the pial surface and surface correspondence-based methods yield the best model fit overall.**  
 505 **a-e** Exceedance probabilities for each combination of source space orientation (pial, white matter, and combined) and location  
 506 (pial, white matter, and combined) models for each dipole orientation vector method tested (**a** downsampled surface normals, **b**  
 507 cortical patch statistics, **c** original surface normals, **d** link vectors, **e** variational vector field) using surfaces derived from  $800\mu\text{m}^3$   
 508 MPM volumes. In each panel the top and right plots show exceedance probabilities for models grouped by source space location  
 509 or orientation model alone.  
 510 **f** As in **a-e**, for each source space orientation and location models over all dipole orientation vector methods.  
 511 **g** Exceedance probabilities for each source space orientation model over all source space location models and dipole orientation  
 512 vector methods (top), for each source space location model over all source space orientation models and dipole orientation  
 513 vector methods (middle), and for each dipole orientation vector method over all source space orientation and location models  
 514 (bottom).

515  
 516 To compare source space surface location and orientation models, we used random effects family level  
 517 Bayesian inference (Penny et al., 2010) over the results from visual ERF 1 and 2 and the motor ERF in all  
 518 participants. This method groups models into ‘families’, and then combines the evidence of models from  
 519 the same family to compute the exceedance probability (EP) for each model family. This corresponds to  
 520 the belief that a particular model family is more likely than the other model families tested, given the  
 521 data from all participants. We first compared combinations of source space location and orientation  
 522 surface models within each method, and found that for most dipole orientation methods (downsampled  
 523 surface normals, cortical patch statistics, original surface normals, and variational vector field), the best  
 524 source orientation space model was the pial surface and the best source space location model was the  
 525 white matter surface (downsampled surface normals EP = 0.708, cortical patch statistics EP = 0.968,  
 526 original surface normals EP = 0.924, variational vector field EP = 0.975; **Figure 7a-c,e**). For the link

527 vectors method, the best source space location model was the white matter surface, and the pial and  
528 white matter source space orientation models were nearly indistinguishable (pial orientation model EP =  
529 0.458, white matter orientation model EP = 0.468; **Figure 7d**). This was not unexpected because the  
530 orientation vectors generated from these surfaces using the link vectors method are exactly 180° to  
531 each other. Over all dipole orientation methods, the best source space orientation surface was the pial  
532 surface and the best source space location model was the white matter surface (EP = 0.654; **Figure 7f**).  
533 We then grouped models into families based on the source space surface used for orientation and  
534 location. This confirmed that the models using the pial surface to compute dipole orientation provided  
535 the best model fit, with an EP of 0.608 (white matter surface EP = 0.379), and models using the white  
536 matter surface to define source space locations outperformed the others, with an EP of 0.985 (**Figure**  
537 **7g**). Finally, we grouped models based on the method used to compute dipole orientation vectors and  
538 confirmed that the link vectors and variational vector field methods were the best overall, with EPs of  
539 0.918 and 0.064, respectively (**Figure 7g**). Using surfaces obtained from 1mm<sup>3</sup> T1 volumes yielded the  
540 same results (**Figure S4**).

541

542

543 **Discussion**

544 In this paper we show that methods for computing dipole orientation which are based on establishing  
545 correspondences between white matter and pial cortical surfaces dramatically outperform methods  
546 based on the geometry of a single cortical surface in fitting evoked visual and motor responses. To this  
547 end, we compared five different approaches for estimating dipole vector orientation, both in  
548 simulations and visual and motor evoked MEG responses.

549 Our results show substantial variation in dipole vector orientation across the different methods. This  
550 indicates that the choice of method is likely to significantly impact the quality of source estimation. At  
551 low SNR levels and with head movements commonly observed in conventional MEG recordings, this  
552 influence is small or non-detectable. However, with the increased SNR and reduced head movements  
553 afforded by high-precision MEG (Meyer et al., 2017; Troebinger et al., 2014b), these differences become  
554 distinguishable when average angular errors between methods vary by around 15 degrees. These small  
555 orientation errors put a hard limit on any possible improvements in non-invasive estimates of cortical  
556 current flow. For example Hillebrand & Barnes (2003) showed that small orientation errors resulted in  
557 localization errors which increased monotonically with SNR.

558 This means that with higher precision MEG recordings, accurate estimation of the dipole orientation  
559 becomes increasingly important. Consequently, conventional approaches which estimate vector  
560 orientation from a single (downsampled) surface, and based on lower resolution MRI volumes, are likely  
561 to offer limited accuracy in source estimation, at least for evoked fields, as analyzed here. By contrast,  
562 methods that utilize link vectors between pial and white matter surfaces constructed from higher  
563 resolution structural images perform significantly better in explaining observed evoked responses.

564 The average angular differences between the five methods compared here were substantial, with  
565 means of 18-30 degrees, both in high-resolution MPMs and in commonly used T1-weighted structural

566 images with  $1\text{mm}^3$  spatial resolution. We do not know the ground truth of current flow orientation in  
567 the brain, but we show here that the average angular difference between methods is within the range  
568 distinguishable in simulated data with SNR and co-registration error levels achievable with high  
569 precision MEG. We were therefore able to compare these methods in terms of how well they fit human  
570 MEG data, leveraging the free energy metric, in order to determine which method best estimates true  
571 dipole orientations.

572 We were surprised by the large variation in orientation estimates from the same anatomy using  
573 different methods. The typical expected orientation differences between methods was  $\sim 20\text{-}30$  degrees.  
574 This in turn led to differences in estimated source location of  $\sim 5\text{-}14\text{mm}$ . In this study we sought to  
575 minimize head-movement and co-registration errors by using head-casts, but in typical MEG studies  
576 such additional errors will only add to this variation. Based on these estimates it would seem that if  
577 precise anatomical information (e.g. from high resolution MRI volumes) is not available then an  
578 approach using some form of loose orientation constraint is advisable (Lin et al., 2006). However, one  
579 advantage of being able to exploit anatomical information is to use the sensitivity of MEG to cortical  
580 orientation to refine the source localization.

581 While the family of source space location models based on the white matter surface yielded the highest  
582 exceedance probability, the results of the surface comparison varied by evoked response and dipole  
583 orientation computation method. Evoked responses can be broken down into temporally dynamic  
584 components and therefore may be the result of a complex temporal pattern of signals in both deep and  
585 superficial cortical layers. We here used the same 100ms time window for source inversion in all  
586 participants and therefore this analysis did not take into account between-participant differences in the  
587 timing of evoked responses and could not track the time course of laminar activity. The inherent  
588 differences between induced and evoked responses may therefore explain the more variable attribution  
589 of the evoked response to pial and white matters surfaces, compared to the bias of high- and low

590 frequency signals towards deep and superficial cortical laminae, respectively (Bonaiuto et al., 2018a).  
591 Future extensions of this work could utilize source inversion in successive time bins to address this  
592 limitation and generate temporally resolved estimates of laminar activity.

593 We assumed the sensor level covariance matrix to be diagonal. However, an independent sensor  
594 dataset recorded during a similar time period in an empty room, showed off-diagonal structure (**Figure**  
595 **S5**). Importantly, the same pattern of model comparison results was obtained when using a sensor  
596 covariance matrix based on these noise measurements (**Figure S6, S7**).

597 In this work, we used free energy as our metric of model fit but we would expect these findings to  
598 generalize across other metrics. For example, we have previously shown that for model comparison  
599 problems of the type utilized in this study, free energy is very highly correlated with nonparametric cross  
600 validation error measures of model fit (Bonaiuto et al., 2018b).

601 The present findings do not just impact high SNR MEG recordings obtained with cryogenic sensors, but  
602 also for new generations of cryogen-free MEG sensors (optically-pumped magnetometers; OPMs). These  
603 sensors can be worn on the head and permit long-duration recordings without head-to-sensor  
604 movement, with accurate knowledge of each sensor's position with respect to the brain (Boto et al.,  
605 2018, 2017; Holmes et al., 2018; Iivanainen et al., 2019, 2017; Knappe et al., 2014). Our results show  
606 that source estimation for this type of recordings is likely to benefit from methods that estimate vector  
607 orientation based on white matter – pial surface vertex correspondences, as opposed to more  
608 commonly used techniques employing a single surface.

609 We here assumed that straight vectors provide the best approximation of the orientation of cortical  
610 columns that generate MEG data. However, cortical columns are often curved (Bok, 1929). In future  
611 work, the curvature of cortical columns could be approximated using sequences of straight vectors  
612 computed from laminar equivolumetric surfaces (Waehnert et al., 2014; Wagstyl et al., 2018). If each

613 vector was tangential to the corresponding segment of the actual (curved) cortical column, this would  
614 result in a piecewise linear estimate of column shape, which may allow more precise source localization  
615 (Bonaiuto et al., 2018b, 2018a; Troebinger et al., 2014a). This development would benefit from higher  
616 resolution (e.g. 7 Tesla) MRI scans, as well as cytoarchitectonic data from histological sections (Amunts  
617 et al., 2013; Wagstyl et al., 2018). The current paper provides a novel framework and set of baselines for  
618 *in vivo* evaluation of the impact of future columnar models on source modeling.

619 Our results are likely to impact other methods which require accurate estimation of cortical surfaces and  
620 the orientation of surface normal vectors. For example, current flow modelling techniques that estimate  
621 the distribution of current delivered with non-invasive brain stimulation approaches such as transcranial  
622 direct current stimulation (tDCS; Bestmann and Walsh, 2017; Bestmann and Ward, 2017) estimate the  
623 normal component of the electric field across the cortical surface, and relate this component to the  
624 observed physiological changes elicited by tDCS (e.g. Laakso et al., 2019; Seo and Jun, 2019). We expect  
625 that improved surface segmentation approaches and vector estimation, as introduced in our present  
626 study, will provide more accurate estimates of these normal components. This will be relevant for  
627 explaining how current delivery via tDCS impacts on physiological and behavioral responses, and  
628 whether the normal component of the electric field is indeed important to explain these effects.

## 629 **Conclusion**

630 Based on the results of our model comparisons, we have shown that, for evoked responses, source  
631 inversion using source locations on the white matter surface and dipole orientation priors computed  
632 using link vectors outperforms the other source location and orientation computation methods we  
633 tested. We therefore recommend that this approach be used as the default in source inversion.

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