

1           **Neural activity precedes conscious awareness of being in or out of a**  
2   **transient hallucinatory state**

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34 **Summary**

35 **(203 words)**

36 Auditory verbal hallucinations, or "hearing voices", is a remarkable state of the mind,  
37 occurring in psychiatric and neurological patients, and in a significant minority of the general  
38 population. An unexplained characteristic of this phenomenon is that it transiently fluctuates,  
39 with coming and going of episodes with time. We monitored neural activity with BOLD-  
40 fMRI second-by-second before and after participants indicated the start and end of a transient  
41 hallucinatory episode during the scanning session by pressing a response-button. We show  
42 that a region in the ventro-medial frontal cortex is activated in advance of conscious  
43 awareness of going in or out of a transient hallucinatory state. There was an increase in  
44 activity initiated a few seconds before the button-press for onsets, and a corresponding  
45 decrease in activity initiated a few seconds before the button-press for offsets. We identified  
46 the time between onset and offset button-presses, extracted the corresponding BOLD time-  
47 courses from nominated regions-of-interest, and analyzed changes in the signal from 10  
48 seconds before to 15 seconds after the response-button was pressed, which identified onset  
49 and offset events. We suggest that this brain region act as a switch to turn on and off a  
50 hallucinatory episode. The results may have implications for new interventions for intractable  
51 hallucinations.

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53 **Main text: 2661 words**

54 **Introduction**

55 Auditory verbal hallucinations (AVH) in the sense of "hearing voices" in the absence of a  
56 corresponding auditory source, is a remarkable state of the mind. AVHs were traditionally  
57 seen as a hallmark of schizophrenia<sup>1-7</sup>, but also occur in other psychiatric and neurological  
58 disorders. AVH cross the border between pathological and normal states of mind, since they  
59 are experienced in about 10% of the general population<sup>8-11</sup>. As a symptom, AVHs are often  
60 experienced as highly distressing, while people in the general population are usually not  
61 distressed to the same degree<sup>12,9</sup>. An equally remarkable characteristic of AVHs is that they  
62 are spontaneous episodes for which there are no known environmental triggers, occurring in  
63 resting and relaxed as well as in stressful and noisy environments<sup>13,14</sup>. The same is true for the  
64 offset of an episode, which likewise can occur in a variety of environmental situations. The  
65 absence of environmental causes for these transient on- and off-fluctuations of AVHs would  
66 thus point to an internal, i.e. some kind of neural switching mechanism, not only for the  
67 spontaneous onset, but also for the spontaneous offset of an episode. We therefore studied the  
68 neural underpinnings of the spontaneous switching between AVH on- and off-states by  
69 monitoring neural activity a few seconds before and after reported onset (start) and offset  
70 (stop) of a hallucinatory episode, and related this to the corresponding conscious awareness of  
71 the event. Brain activity can be monitored on-line with functional magnetic resonance  
72 imaging (fMRI), where changes in neural activity are estimated from modelling of the blood-  
73 oxygenation-dependent (BOLD) function<sup>15</sup>. Yet this requires participants to lay still in the  
74 scanner while experiencing AVH and indicating their on and offset by button-press, a very  
75 demanding task (see<sup>9,16-19</sup>). This paradigm requires patients to be aware and thoughtful of  
76 their experiences and to experience a required minimum of episodes of AVH during the  
77 scanning session, as neither continuous hallucinations nor a period with too few

78 hallucinations will allow the study of on- and offsets. Only few research groups around the  
79 world have succeeded to obtain a number of such scans, typically less than 20. In order to  
80 increase power to detect subtle changes in activity during brief moments of on and offsets, we  
81 joined forces from three research groups to recruit a reasonably large sample of individuals  
82 who were hallucinating frequently, but not continuously. The aim of the present study was to  
83 use fMRI to monitor changes in neural activity on a second-by-second-basis, in a resting-state  
84 situation, where subjects signaled the onset of a hallucinatory episode by pressing one  
85 response-button and the offset of an episode by pressing another response-button, in the  
86 course of the scanning session. A time-window was set from 10 seconds before to 15 seconds  
87 after the subject had pressed a button, from which voxel-wise data were extracted, analyzed  
88 and displayed second-by-second in a sliding window over the evaluation period (see  
89 Methods). Data were pooled from three different sites at the University of Bergen, Norway,  
90 Groningen University Medical Center, Netherlands, and Medical University of Plovdiv,  
91 Bulgaria, making up a total of 66 subjects hallucinating during fMRI recordings. As  
92 hallucinatory experiences cross the border between abnormal and normal conditions, we  
93 included both clinical and non-clinical "voice-hearers", focusing on tracking the neural  
94 signatures of AVH-experiences per se, not restricted to a particular diagnostic group or mental  
95 condition.

96

## 97 **Results**

### 98 *Anticipated activity patterns during hallucinatory periods*

99 Functional data that were obtained using the button-press symptom-capture paradigm<sup>9</sup>  
100 revealed several statistically significant clusters of increased activity during hallucinatory  
101 periods (i.e. periods after onset and before offset). These clusters included the left fronto-  
102 temporal language areas (Wernicke's area in the superior temporal gyrus, and Broca's area in

103 the inferior frontal gyrus), using a FEW-corrected significance threshold of  $p < .05$  (see Figure  
104 1 and Table 1).

105 -----

106 Insert Figure 1 OVERLAPPING ACTIVITY about here about here

107 -----

108 We compared the anatomical localizations of these activity with areas previously reported as  
109 activated during ongoing hallucinatory episodes (see meta-analysis<sup>16, 17</sup>). As can be seen in  
110 Figure 1, the overlap of the present activity with previous reports is almost perfect, thus  
111 validating that the present activity reflects neural correlates of ongoing hallucinations.

112 Analyzing activity data from each of the three sites separately, the general pattern of activity  
113 remained, although statistically weaker for the Bergen cohort and reduced to trend level for  
114 the Plovdiv cohort. Contrasting clinical- and non-clinical voice hearers from the Groningen  
115 cohort revealed overlapping activity in all areas except for the right planum temporale (PT)  
116 and right lateral superior occipital cortex.

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118 Insert Table 1 about here

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120

121 *Differential activity in the ventro-medial frontal cortex*

122 Analysis of the extracted time-courses from the nominated regions of interest (ROIs),  
123 separately for onset and offset of episodes, revealed a distinct decrease in activity in the  
124 intersection of the paracingulate cortex, medial frontal cortex, and the frontal pole (see Figure  
125 2). The decrease had a minimum peak at time ( $t$ ) = 3 sec ( $\Delta = -158$  iu,  $p = 0.021 \pm 0.002$ ,  
126 95% CI) relative to the button-press response (see Figure 3). This minimum preceded the

127 corresponding motor response from the subjects' button-press which had a peak maximum at  
128  $t = 5$  seconds.

129 -----

130 Insert Figure 2 ANATOMY OF ROI about here

131 -----

132 The decrease in activity preceding an offset button-press contrasted to an increase in activity  
133 observed in advance of an onset button-press ( $\Delta = 35$  iu,  $p = 0.014$ ,  $\pm \sim 0.0016$ , 95% CI),  
134 occurring at around  $t = -1$  second. These results were verified in an extended time-series  
135 analysis (see Figure 4) averaged across subjects, and where aberrant time-courses were  
136 rejected and results iteratively updated. An HRF-model fit was thereafter applied to the data,  
137 revealing a similar differential pattern for onset- and offset-events as seen in Figure 3. See  
138 Methods section for further details.

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140 Insert Figure 3 TIME-COURSE about here

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143 Insert Figure 4 ITERATIVE ANALYSIS about here

144 -----

145 These results were obtained using the strictest criteria for interpretation of the subjects'  
146 button-press response data, and were maintained (with varying levels of significance) for  
147 more liberal interpretations ( $\Delta = -79$  iu,  $p = 0.16$ ,  $\pm \sim .005$ , 95% CI,  $\Delta = 36$  iu,  $p = 0.0024$ ,  
148  $\pm \sim .0007$ , 95% CI for the long-block interpretation, see Methods for explanation). ROIs in the  
149 in the pre-central motor-area also exhibited significantly increased activity, with peak activity  
150 at  $t = 5$  seconds; all significances after FEW-correction and p-level set to  $< .05$ .

151

152 *4D permutation analysis*

153 Full-volume permutation analysis across the nominated time-windows further confirmed a  
154 differential direction of activity for offsets versus onsets at the ventral edge of the intersection  
155 of the paracingulate cortex, medial frontal cortex and the frontal pole (see Figure 2). This  
156 region exhibited significantly reduced activity ( $p = 2.5 \times 10^{-8}$ ) for offset-of-hallucination events  
157 relative to onset-of-hallucination events, peaking 2 seconds after the recorded button-press  
158 event, and 3 seconds before the peak of the motor activity associated with the button-press  
159 itself. Additional contrasting activity, not directly attributable to the motor response, was  
160 observed in the inferior frontal gyrus ( $p = 1.4 \times 10^{-11}$ , with peak at time (t) = 17 sec), and the  
161 central opercular cortex bordering on Heschl's gyrus ( $p = 4.6 \times 10^{-14}$  with peak at time (t) = 19  
162 sec). These regions were also identified in our functional block-analysis (see Table 1), and  
163 have also been mentioned in the literature<sup>16,17</sup> (see Table 1).

164

165

166 The subsequent permutation analysis of offset-of-hallucination events against “baseline” data  
167 from random time-windows showed again significantly reduced activity ( $p = 5.2 \times 10^{-7}$ )  
168 specific to offset-of-hallucinatory events. This analysis also revealed transient increases in  
169 activity in the anterior cingulate ( $p = 3.7 \times 10^{-6}$ ), insula/left operculum ( $p = 9.3 \times 10^{-6}$ ), thalamus  
170 ( $p = 1.8 \times 10^{-7}$ ) and paracingulate cortex ( $p = 1.8 \times 10^{-7}$ ). Permutation analysis with onset-of-  
171 hallucinatory events against “baseline” data also revealed a slight increase in activation  
172 initiated before the button-press with a peak around 1 second after the button-press event ( $p =$   
173  $2.5 \times 10^{-4}$ ). Finally, there was a large and significant increase in activity in the primary motor  
174 cortex in the pre-central gyrus ( $p = 7 \times 10^{-32}$ ), representing the button-press response per se.

175

176 **Discussion**

177 The finding of anticipatory neural activity in the ventro-medial frontal region preceding start  
178 and end of auditory hallucinations is a novel finding, which could lead to new hypotheses  
179 about excitation and in particular inhibition of a hallucinatory event, and what underlies the  
180 experience of the start and stop of a "voice". Both the time-course- and permutation-analyses  
181 revealed a significant brain response initiated a few seconds in advance of the subject  
182 becoming consciously aware of being in or out of a hallucinatory state. This suggests that the  
183 ventro-medial frontal region may be crucial in both the initiation and cessation of  
184 hallucinatory episodes, and speaks to a kind of regulatory role, or switch function for this  
185 region. Metaphorically, it could be thought of as this region acting like a conductor, directing  
186 the orchestration of neural events that leads up to a full-blown perceptual experience of  
187 "hearing a voice" in the absence of a corresponding external source and also to the cessation  
188 of the perceptual experience. Brain responses in advance of conscious awareness have been  
189 previously reported for error monitoring, where subjects showed reduced activity in regions  
190 related to the default mode network (the "oops region") seconds before they became aware of  
191 having made an erroneous response<sup>20</sup>. The present results complement recent findings of  
192 aberrant functional connectivity<sup>21</sup> and morphological differences<sup>22</sup> in the same brain region.  
193 Garrison, et al.<sup>22</sup> used structural MRI and found that hallucinating patients had shorter  
194 paracingulate sulcus than healthy controls and also to non-hallucinating patients, and  
195 suggested that this region of the brain is tuned to "reality monitoring", i.e. the ability to judge  
196 whether a memory comes from an outer or inner source. This suggestion<sup>22</sup> was based on the  
197 findings reported by Buda, et al.<sup>23</sup> that otherwise healthy individuals, born without a  
198 discernible paracingulate sulcus in either hemisphere, showed impaired performance on a  
199 word-pair memory/imagery task. These observations<sup>22,23</sup> may provide important clues for  
200 understanding the significance of the present findings, insofar that the ventral portion of this  
201 cortical region may be crucial for how AVHs are spontaneously initiated and also why they



202 may spontaneously and transiently disappear. In this respect our data support a previous  
203 report from two patients of anticipatory neural activity to onset-signaling<sup>24</sup>. A potential  
204 confounding of the results could be anticipatory attention focus on motor-responses (cf.<sup>25</sup>),  
205 which otherwise could affect the observed activity. As seen in the lower panels of Figure 3  
206 this is probably not the case, since there was a clear peak around 5 seconds post-response  
207 obtained from the pre-central motor-cortex on the left side (from right-handheld response-  
208 buttons), and with 5-6 times higher response amplitude as that obtained from the ventro-  
209 medial frontal cortex<sup>26</sup>. This is what one would expect considering the lag of the  
210 hemodynamic response relative to a neural event, but would not expect for a peak occurring  
211 at 3-4 seconds and in the ventro-medial frontal cortex, after the button-press. The decrease in  
212 brain activity a few seconds before the indicated awareness of the offset of a hallucinatory  
213 episode, may correspond to previous findings of frontal neurotransmitter imbalance<sup>27-29</sup>.  
214 Using MR spectroscopy (<sup>1</sup>H-MRS), Ćurčić-Blake, et al.<sup>30</sup>, van Den Heuvel, et al.<sup>31</sup> and  
215 Hugdahl, et al.<sup>32</sup> found increased levels of glutamate in frontal regions in hallucinating  
216 individuals. This is in accordance with what Jardri, et al.<sup>28</sup> labelled the Excitatory/Inhibitory  
217 (E/I) imbalance model of auditory hallucinations, and we now suggest that the offset of a  
218 hallucinatory event is mediated by temporary restoring such imbalances. Future research will  
219 hopefully resolve the underlying causes at the receptor and transmitter level. The present  
220 findings could also have therapeutic implications in guiding more targeted brain stimulation  
221 approaches. Brain stimulation interventions is a promising approach to medication-resistant  
222 hallucinations<sup>33,34,35</sup> and targeting the the ventro-medial frontal cortex using stimulation to  
223 stop the onset, or accelerate the offset of an AVH-episode could be a way to help patients  
224 overcome intractable AVHs.  
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354 **Table 1**

355 **Table 1** shows clusters and local maxima obtained by block analysis in the present study,  
 356 with corresponding activations from Jardri, et al.<sup>16</sup> and Kompus, et al.<sup>17</sup>. Clusters in the novel  
 357 data are thresholded non-parametrically at  $Z > 4.5$ ; corrected cluster significance is reported,  
 358 thresholded at  $p > 0.05$  and extent  $> 20$  voxels.

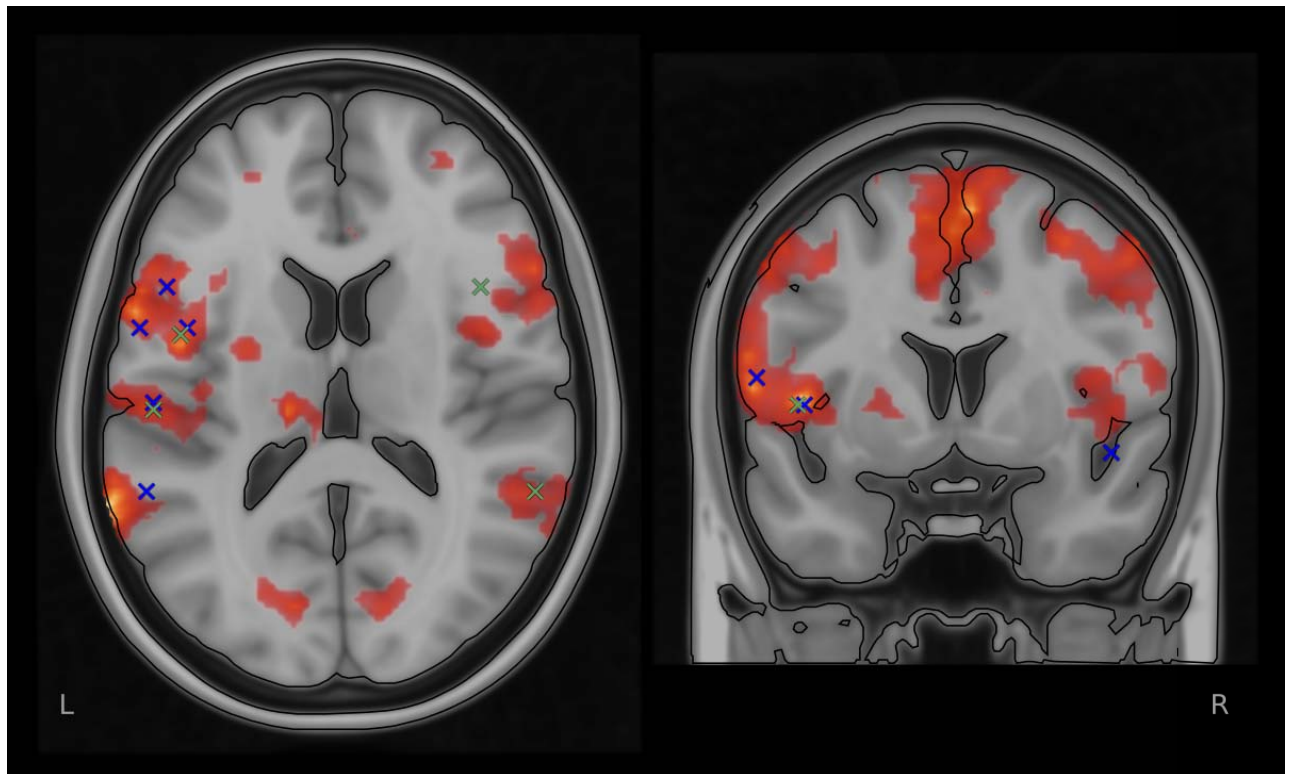
359

Present Study	p	ext	MNI coord (mm)			Jardri et al. [16]	MNI coord (mm)			Kompus et al. [17]	MNI coord (mm)		
			x	y	z		x	y	z		x	y	z
Inferior Frontal Gyrus, pars opercularis	BA44 L	3.8x10 <sup>-4</sup>	43	-56	12	8	A Broca's convolution			-50	13	5	
Precentral Gyrus	BA44 L		-58	6	9		Precentral gyrus			-57	2	13	
Central Opercular Cortex/Insula	BA44 L	5.8x10 <sup>-5</sup>	65	-44.8	0.7	5.1	Anterior insula			-44	2	3	Insula
Thalamus	L	3.7x10 <sup>-4</sup>	21	-13	-22.5	7.5	B Hippocampus/ parahippocampal gyrus			-26	-31	-10	Hippocampus
Inferior Frontal Gyrus, pars opercularis	BA45 R	7.4x10 <sup>-5</sup>	55.8	19.6	4.8		C Anterior insula			47	10	-10	Inferior frontal gyrus
							Frontal Operculum			44	17	-17	Superior frontal gyrus
							D Superior and middle temporal gyri			-56	-45	14	
Supramarginal Gyrus, posterior division	BA22 L	5.3x10 <sup>-7</sup>	97	-65.2	-50	18.7	E Supramarginalis gyrus			-55	-20	14	Inferior parietal lobule
Postcentral Gyrus	BA2 L	6.3x10 <sup>-13</sup>	396	-52	-23.3	38.7							Superior temporal gyrus
Postcentral Gyrus	BA2 L		-49.7	-28.5	47.4								Middle temporal gyrus
Central Opercular Cortex		1.2x10 <sup>-5</sup>	86	-53.4	-22.7	22							Middle temporal gyrus
													Cerebellum lobule V
Precentral Gyrus	BA6 L	7.7x10 <sup>-7</sup>	125	-56	-6	51							
Precentral Gyrus	BA6 L		-50	-3.5	50								
Precentral Gyrus	BA6 L		-53	-2	45								
Juxtapositional Lobule	BA6 R	4.6x10 <sup>-13</sup>	403	1.5	-2.8	57							
Juxtapositional Lobule Ctx	BA6 R		4.7	8.7	64								
Juxtapositional Lobule Ctx	BA6 R		5	6	60								

360 **Figure 1**

361

362 **Figure 1** shows the results from the standard group-level block-analysis of the BOLD-fMRI  
363 data, overlaid with peak activity from the Jardri, et al.<sup>16</sup> and Kompus, et al.<sup>17</sup>, meta-analyses,  
364 marked respectively with a blue (Jardri) and green (Kompus) 'x', verifying the presently seen  
365 activity with activity previously repeatedly reported in the literature.



366

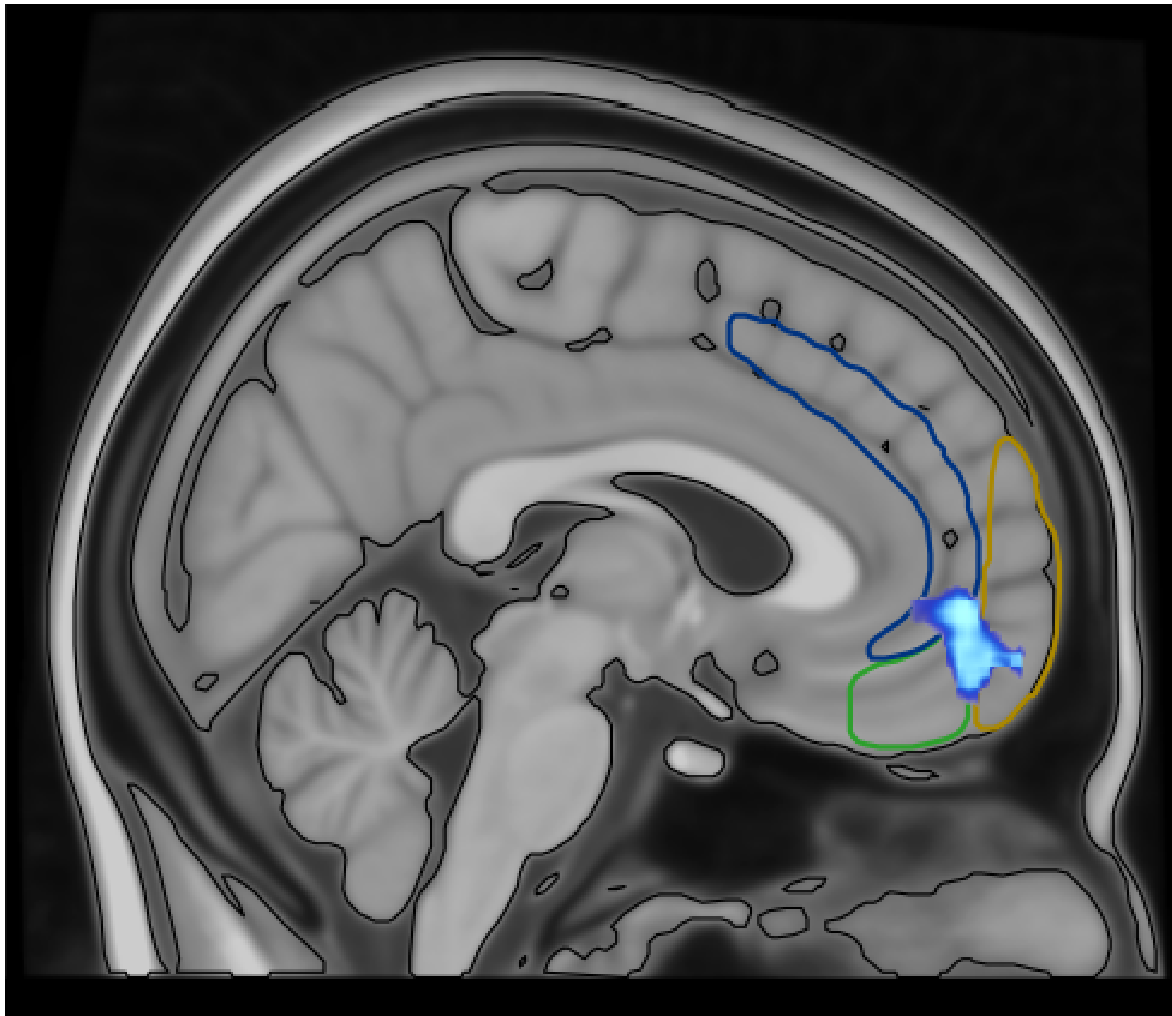
367

368 **Figure 2**

369 **Figure 2** shows the anatomical localization of the ROI (turquoise) with MNI peak coordinates  
370  $x=8.8$ ,  $y=44.8$ ,  $z=-5.64$  mm from where the time-courses were extracted, in the intersection of  
371 the paracingulate cortex (demarcated in dark blue), medial inferior frontal cortex (demarcated  
372 in green) and frontal pole (demarcated in yellow).

373

374



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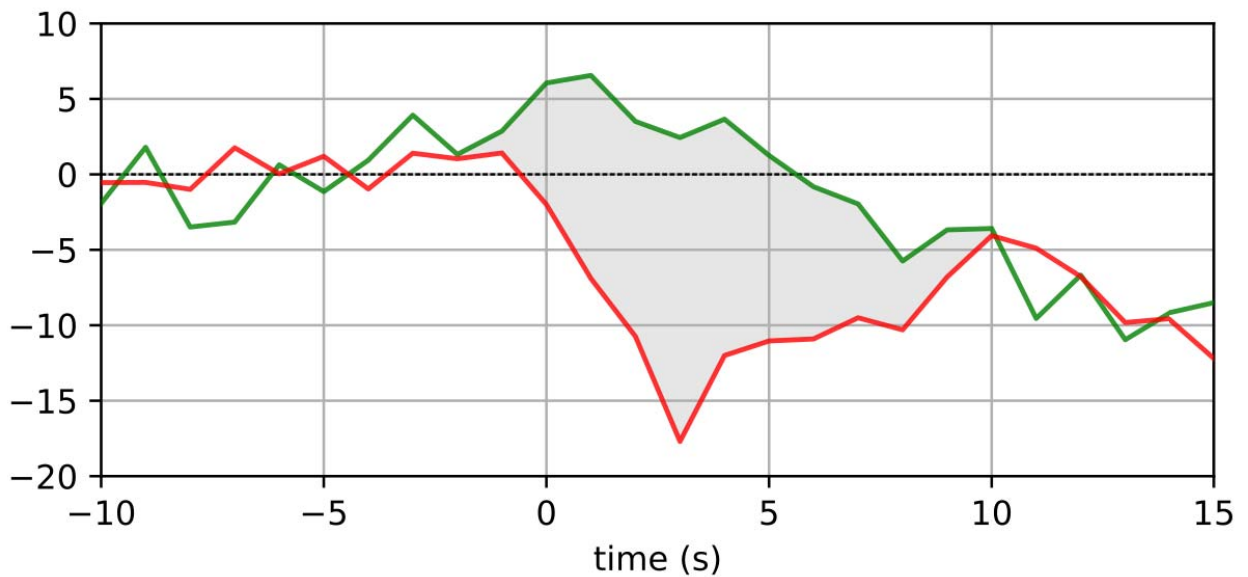
376

377 **Figure 3**

378 **Figure 3** shows filtered time-courses tracked second-by-second around the onset-of-  
379 hallucination (red) versus offset-of-hallucination (green) events from the ROI at the  
380 intersection of the paracingulate cortex/medial inferior frontal cortex/frontal pole. Grey area  
381 shows differential responding for onset- versus offset-events. Time "0" on the x-axis represent  
382 the point in time when the button-press occurred. Time -10 represent 10 secs before a button-  
383 press and time 15 represents 15 sec after a button-press. Y-axis in international units (iu). See  
384 Results section for further details.

385

386



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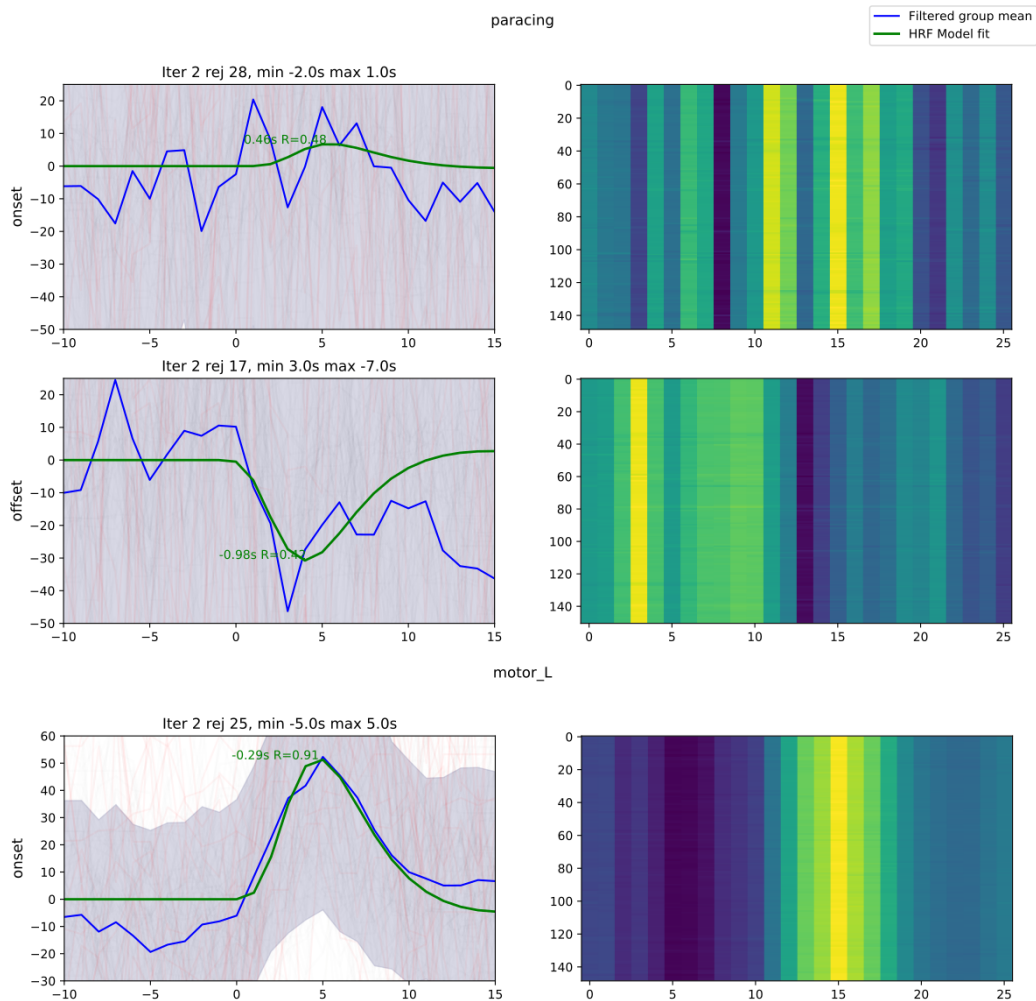
388



389 **Figure 4**

390 **Figure 4** shows group-average (blue line) and hemodynamic response function (HRF) -  
391 model fit (green line) of time-course data from the nominated ROI in the intersection of the  
392 paracingulate cortex/medial inferior frontal cortex and the frontal pole, separated for onset  
393 (left upper panel) and offset (left middle panel) events, for the final iteration of filtering. The  
394 lower panel show corresponding time-courses for the left pre-central motor cortex (note  
395 different y-axis scale). Adjacent panels to the right show group-mean encoded as intensity, for  
396 each step (y-axis) of a leave-one-out validation according to which strongly deviant time-  
397 courses were rejected. See Methods and Results sections for further details.

398



399



401 **Figure 5**

402 **Figure 5** illustrates the three possible interpretations of subjects' response patterns. Pattern A

403 is unambiguous, and is matched identically by strict, short and long definitions. Pattern B

404 includes a spurious "offset" event; the strict definition rejects this block, the short definition

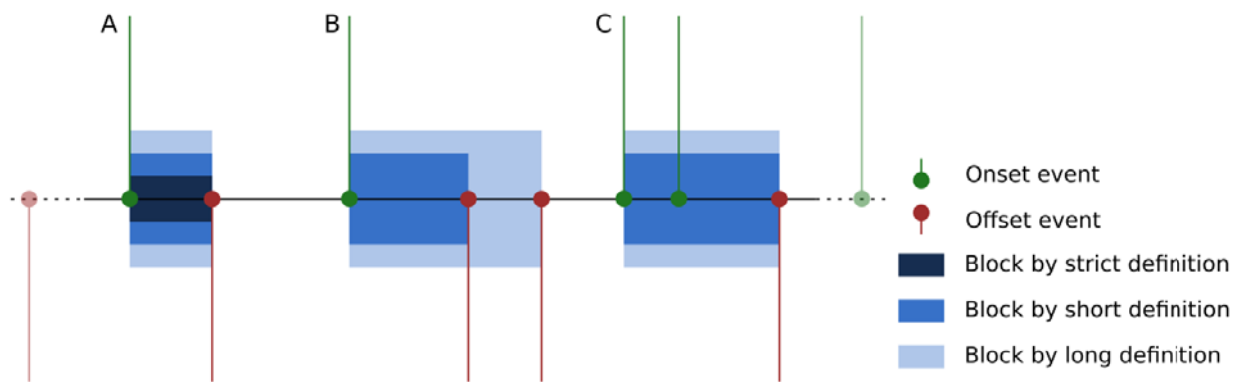
405 ends the block at the first offset, and the long definition ends the block at the last offset.

406 Pattern C shows spurious onset events; again this block was rejected by the strict definition,

407 whilst both short and long definitions match from the first "onset" event.

408

409



411

412

413

## Methods

### 414 Subjects

415 Structural data and functional BOLD data were collected from a total of 66 subjects, of which  
416 45 were diagnosed with an ICD-10 or DSM-IV schizophrenia spectrum disorder. The patients  
417 came from three collaborating projects and sites. These were University of Bergen, Norway  
418 (n=11, 7 males, mean age 27.8 (SD 7.0) years); Plovdiv Medical University, Bulgaria (n=13,  
419 11 males, mean age 35.3 (SD 14.0) years), Groningen University Medical Center, Netherlands  
420 (n=21, 7 males, mean age 39.0 (SD 11.4) years), total 25 males and 19 females, mean age  
421 37.9 (SD 13.2) years. Symptom severity for patients was assessed with the positive and  
422 negative syndrome scale (PANSS<sup>36</sup>). Mean total PANSS score was 64.9 (SD 16.9). In order to  
423 be included in the study, patients had to score >3 on the PANSS, P3 hallucinatory behavior  
424 item within a week of the MR scanning (mean P3 score 4.6 (SD 1.1)). The patients were all  
425 on second-generation antipsychotics (often clozapine), with some patients in addition being  
426 prescribed antidepressants and/or anxiolytics. Mean antipsychotic Defined Daily Doses  
427 (DDD) were 1.228 (SD 0.578). The total sample also consisted of 21 non-clinical  
428 hallucinating individuals (4 males, mean age 44.5 (SD 13.0) years), i.e. in whom a clinical  
429 axis I and axis II diagnosis was ruled out using the CASH and SCID-II interview, included in  
430 the Groningen University Medical Center sample (for details see<sup>10</sup>). This yielded a total  
431 sample of 29 males, 37 females, mean age 38.2 (SD 13.0) years. The study was approved by  
432 the local ethics committees at each site, and had a European Research Council Ethics  
433 Approval (ERCEA 2016-439428). Transfer of data between the sites and re-analysis at the  
434 Bergen University was approved by the ethical committees at each site, and further confirmed  
435 by the Regional Committee for Medical Research Ethics in Western Norway (REK-Vest  
436 #2017/933).

437

438 **Data collection**

439 Functional MR data were collected with a “symptom-capture” paradigm<sup>9</sup>, where subjects  
440 were instructed to press a button when a hallucinatory episode began (onset), and to press  
441 another button when the episode ended (offset). The instruction of when to press the buttons  
442 was presented visually through LCD goggles mounted on the head-coil, in the language  
443 appropriate to the location, along with a fixation cross that was displayed in the middle of the  
444 visual field. A time-window was set from 10 seconds before to 15 seconds after the subject  
445 had pressed a button, from which voxel-wise data were extracted, analyzed and displayed in a  
446 sliding window over the evaluation period. Particulars of the acquisition varied between sites.  
447 Gradient Echo Planar Imaging (EPI) was used to collect functional BOLD data on all sites.  
448 Data from Bergen were collected using a 3T GE 750 scanner with a 32-, or 8-channel head  
449 coil (300 volumes at TR = 2000 ms, total duration 10 min, TE = 30 ms, flip angle 90°,  
450 resolution 128 x 128, pixel spacing 1.72 mm, 30 or 26 slices of 3mm thickness with 0.5mm  
451 gap). Plovdiv data were collected with a 3T GE 750w scanner and 24-channel head coil (900  
452 volumes at TR=2000 ms (total duration 30 min), TE = 30 ms, flip angle 90°, resolution 64 x  
453 64, pixel spacing 3.44 mm, 34 slices of 3 mm thickness with 0.5 mm gap). Groningen data  
454 were acquired on a 3T Philips Achieva scanner, as 800 volumes at TR = 21.75 ms (total  
455 duration 8 min, 6 sec), TE = 32.4 ms, 64 x 64, 4 mm voxel size, 40 slices (4 mm thickness),  
456 no gap. This scan sequence achieves full brain coverage within 609 ms by combining a 3D-  
457 PRESTO pulse sequence with parallel imaging (SENSE) in two directions using a  
458 commercial 8-channel SENSE head-coil. A high-resolution structural T1 volume was  
459 acquired for each subject, along with additional sequences that varied between sites, of no  
460 relevance and are not reported herein.

461

462 **Motor (button-press) response data**

463 Upon visual inspection of the subjects' button-press data, it was found that a certain number  
464 of subjects reported multiple episode-onsets which did not distinctly match to a single end-of-  
465 "voice" event, which required interpretation and operational definition of episodes. We  
466 interpreted and operationally defined the relationship between onset- and offset button-  
467 responses in three different ways, described and illustrated in Figure 5 below. According to  
468 each definition, subjects' button-press response-data were filtered to remove spurious  
469 episodes, and extract distinct blocks of hallucinatory vs non-hallucinatory periods. Additional  
470 criteria regarding minimal spacing between events ensured the validity of the subsequent  
471 analyses.

472

473 *Operational definition of hallucinatory and non-hallucinatory periods*

474 According to a first possible interpretation and definition, denoted "short blocks",  
475 hallucinatory periods were defined as spanning from the moment a subject first pressed the  
476 button indicating the start-of-voice episode, until they first pressed the button to indicate the  
477 end-of-voice episode. This yielded 1055 usable blocks across all subjects. In a second  
478 interpretation, denoted "long blocks", hallucinatory periods were defined as spanning from  
479 the moment a subject first pressed the button indicating the start-of-voice episode, until the  
480 last press indicating the end-of-voice episode before the next reported start-of-voice episode.  
481 This yielded 1000 usable blocks across all subjects. The final, "strict blocks" interpretation,  
482 accepted only periods unambiguously bounded by a single start-of-voice and a single end-of-  
483 voice button-press. This yielded 300 usable blocks across all subjects. Figure 5 shows the  
484 different interpretations, illustrated on a representative subject's response data.

485 -----

486 Insert Figure 5 DEFINITION OF RESPONSE BLOCKS about here

487 -----

## 488 **Pre-processing of fMRI data**

489 Functional MR data were pre-processed using standard tools from FSL 5.0.11 (FEAT  
490 pipeline), with additional filtering for artifacts using the ICA-AROMA method<sup>37-40</sup>. Brain-  
491 masks for each subject's structural T1-images and functional data were derived using FSL's  
492 bet2 tool, with fractional intensity threshold and initial mesh center-of-gravity tuned on a  
493 group basis to accommodate differences between the three sites. Individual brain-masks were  
494 manually subject to visual quality control to ensure completeness and specificity of the mask.  
495 When necessary, brain masking was repeated for a small number of subjects using  
496 individually tuned parameters. Next, individual brain-extracted functional data were subject to  
497 motion correction, using FSL's MCFLIRT utility<sup>38,41</sup>. Data were filtered spatially with a 5 mm  
498 FWHM Gaussian kernel, and temporally with a 100 sec high-pass filter. They were then  
499 registered to individual, brain-extracted high-resolution structural images using FSL's linear  
500 registration tool (FLIRT), with the recommended Boundary-Based Registration mode and a  
501 restricted (35 degree) search range. Registration was inspected visually for validity; for three  
502 subjects where the BBR method performed poorly, a 12-degree-of-freedom registration was  
503 substituted. Individual brain-extracted high-resolution structural images were registered to a  
504 standard 2mm T1 template in MNI152 space (ICBM152, non-linear, 6<sup>th</sup> generation), with a  
505 12-degrees-of-freedom linear registration using FSL FLIRT, followed by a nonlinear  
506 registration with 10 mm warp resolution using FSL FNIRT. The ICA-AROMA method was  
507 applied to filtered, native-space functional data to remove residual signals associated with  
508 motion artifacts and noise. Finally, per-subject native-space functional masks were  
509 transformed into standard space using non-linear parameters derived from the registration  
510 steps; these masks were assessed programmatically to ensure adequate coverage of the brain,  
511 with particular attention to prescribed regions of interest (ROIs), see below.

512

513 **Block analysis**

514 To confirm the validity of the filtered response data, a standard fMRI block--analysis was  
515 performed using FSL FEAT first-level and higher-level analysis pipelines<sup>42</sup>, applied for the  
516 long block definition. Mixed effects modeling (FLAME 1+2) was used for higher-level  
517 analysis; clusters were thresholded non-parametrically at  $Z > 4.5$ ; corrected cluster significance  
518 thresholded at  $p > 0.05$  and extent  $> 20$  voxels.

519

520 **Time-course analysis**

521 For each hallucinatory period, identified as demarcating the start or end of a hallucinatory  
522 episode, windows of functional data were extracted extending from a time of  $t = -10$  sec  
523 through to  $t = +15$  sec, relative to the moment in time at which the button-press event  
524 occurred (set to  $t = 0$  sec), as a continuous variable. Since the temporal resolution of  
525 functional data is relatively coarse, and also varied between sites in the current dataset, data  
526 were sampled at regular 1sec intervals, weighted and normalized according to a Gaussian  
527 kernel in the temporal dimension (FWHM = 0.94 sec). An initial principal component  
528 analysis (PCA) on grouped, extracted functional segments, guided the selection of ROIs for  
529 further inspection and analysis. Cluster locations identified in the functional analysis and  
530 those nominated and reported in previous meta-analyses<sup>16,17</sup> were also inspected for overlaps  
531 of activity between the current study and activity reported in the meta-analyses (see Figure 1  
532 and Table 1). For each nominated ROI, and for each of the extracted functional segments,  
533 time-course vectors were obtained and spatially averaged over a 5 mm radius sphere,  
534 allowing activity in each region to be examined and evaluated in the time-frame leading up to  
535 and immediately following a button-press, marking the onset and offset of a hallucinatory  
536 episode. Separately for onset and offset events, time-course vectors for each region were  
537 aligned in the temporal dimension to the group-average for the respective region (maximizing



538 cross-correlation). Aberrant time-courses (correlation varying by more than two standard  
539 deviations) were rejected, iteratively updating the group to refine an estimated model time-  
540 course for the region around onset and offset events as shown in Figure 4. A dual-gamma  
541 hemodynamic response-function (HRF) model was thereafter fitted to the refined time-course  
542 model, allowing magnitude and timing of any activity-related peak to be identified and  
543 statistically evaluated. Random permutation-analysis (n = 5000) was performed to identify  
544 differential effects on fit parameters between onset- and offset-events.

545

#### 546 **4D permutation analysis**

547 The ROI-based analysis was generalized to a full four-dimensional (4D) permutation analysis,  
548 characterizing activity specific to onset- or offset-events at each time-point in the extracted  
549 window segments, searching across the entire brain volume voxel-wise. Due to the large  
550 volume of data and computationally intensive nature of the permutation analysis, it was  
551 necessary to develop a new software tool to facilitate this analysis. P-values were extracted (n  
552 = 10,000 permutations), along with p-values calculated on a gamma approximation of the  
553 obtained distribution<sup>43</sup>, for each voxel, at each time-point. Initially, time-windows associated  
554 with onset- and offset-events were contrasted jointly in the permutation analysis, yielding  
555 differential effects for onset and offset events. Subsequently, time-points from offset- and  
556 onset-events were separately contrasted against windows extracted around random time-  
557 points (without synchronization to subjects' button-responses), as a baseline state.

558

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583

584

#### 585 **Data availability statement**

586 The datasets analysed during the current study are not publicly available due to restrictions  
587 imposed by Regional Committee for Medical Research Ethics in Western Norway (REK  
588 Vest) and the Data Protection Officer of the Western Norway Health Authorities  
589 (Personvernombudet) but are available from the corresponding author on reasonable request

#### 590 **Software/Code availability statement**

591 Novel in-house developed software implemented for this study has been made publicly  
592 available here: <https://git.app.uib.no/bergen-fmri/functional-transients>. All other stages of  
593 analysis were performed using widely-available open-source software, including tools from  
594 the FSL suite and additional filtering with the ICA-AROMA method.

#### 595 **Author contributions**

596 KH designed the study, participated in patient recruitment, data analysis and interpretation,  
597 wrote the ms, ARC analyzed the data, participated in data acquisition and interpretation,

598 commented on the ms, EJ participated in patient recruitment, commented on the ms, LE  
599 participated in data acquisition and analysis, commented on the ms, DS participated in patient  
600 recruitment. commented on the ms, SK participated in patient recruitment, commented on the  
601 ms, LBS participated in organization of data and ms and commented on the ms, RAK  
602 participated in patient recruitment, commented on the ms, EML participated in patient  
603 recruitment, commented on the ms, IES participated in patient and subjects recruitment, data  
604 interpretation, and commented on the ms.

### 605 **Supplementary information**

606 Correspondence and requests for materials should be addressed to Kenneth Hugdahl  
607 ([hugdahl@uib.no](mailto:hugdahl@uib.no)).

### 608 **Competing interests**

609 The co-authors Kenneth Hugdahl, Alexander R. Craven and Lars Ersland own shares in the  
610 company NordicNeuroLab, Inc. (<https://nordicneurolab.com/>) that produced add-on  
611 equipment used for BOLD-fMRI data acquisition. All authors declare no conflict of interest.

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614 making the study possible.

615