Event-Related Potentials and Fast Optical Imaging of Cortical Activity During an Auditory Oddball Task



Manon E. Jaquerod, Ramisha Knight, Alessandro E. P. Villa, and Alessandra Lintas

1 Abstract Event-related potentials (ERP) have been repeatedly used to study the

- ² spatiotemporal dynamics of the attentional response in the well-known oddball
- 3 paradigm. We combined electroencephalography (EEG) with frequency-domain
- ⁴ near-infrared spectroscopy (fNIRS) of the frontal cortex to measure neuronal activity
- $_{\scriptscriptstyle 5}$ with a high spatial and temporal resolution. The aim of this study was to determine
- 6 the precise chronology of event-related optical signals (EROS) and their consistency
- 7 with ERPs. In agreement with previous studies, the oddball condition produced larger
- 8 waveforms for rare (1500 Hz pure tone) with respect to frequent stimuli (1000 Hz),
- ⁹ with N1, P2, N2, P3a, and P3b components. At a latency corresponding to the mis-
- ¹⁰ match negativity/N2 wave component, EROS showed the organization of a complex
- activity in a functional network of frontal areas, with rare tones activating the left
- ¹² premotor dorsal cortex and the left inferior frontal cortex and decreasing the activity
- of the right superior frontal gyrus. Rare tones elicited also a strong N500 (N400-like)
- wave component that EROS contributed to localize at the level of the right medial frontal gyrus by EROS. The simultaneous recording of fNIRS and EEG measure-

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¹⁵ ments with high temporal accuracy over the human prefrontal cortex supports the

- ¹⁶ potential for this approach to unravel the functional cortical network involved in
- ¹⁷ cognitive processing.

18 1 Introduction

A fundamental property of animal behavior is habituation, i.e., the decrement of 19 response with repeated stimulation, which is a necessary process to detect deviant 20 or novel stimuli (Blumstein, 2016; Thompson, 2009). A classical paradigm, called 21 "oddball" paradigm, used to study the responsiveness to a repeated auditory stimulus 22 consists of a long sequence of repetitive identical stimuli (the frequent stimuli) that 23 is replaced with a low probability, and at random, by a different stimulus (the rare 24 stimulus). Brain activity elicited by frequent and rare stimuli has been recorded by 25 electrophysiological means to study the brain processes underlying attention switches 26 to, and involuntary discrimination of, rare among the frequent stimuli. Animal studies 27 showed that responses at the level of the cerebral cortex are associated with attentional 28 circuits that are strongly affected during anesthesia (Apelbaum et al., 1960; Eriksson 29 & Villa, 2005; Ruusuvirta et al., 1996). 30

In humans, the oddball paradigm was implemented in active and passive condi-31 tions (Näätänen, 1990; Squires et al., 1975). The active condition is an attentional 32 task, such that the participant must attend to all stimuli in order to detect the rare 33 stimuli and generate a motor response, e.g., a key-press. In the passive condition, 34 the participant is usually instructed to ignore all stimuli and to attend other stimuli, 35 usually presented in another sensory modality. Maintaining a goal-directed behavior 36 that requires selective attention, brain responses to the habituation of the frequent 37 stimuli, and the salient perception of rare stimuli may bring insights about reorien-38 tation of attention. The oddball paradigm has been extensively studied by electroen-39 cephalography (EEG), i.e., by measuring variations in the electric field at the scalp 40 induced by the summation of mass neuronal firing rates with a millisecond-level 41 of resolution. The selective sensitivity of the technique for brain layers with corre-42 lated dipoles makes neural activity in sulci far less represented in the EEG signal 43 than neural activity in gyri (Nunez, 1995). Furthermore, the spatial filtering of fields 44 by the head volume conductor implies interdependencies of measurements between 45 electrode sites and strongly restrain the capacity for EEG to depict the precise spa-46 tial distribution of patterns of activity (Nunez, 1995). The event-related potentials 47 (ERPs) are obtained by averaging, over many trials, the EEG signal variations trig-48 gered by sensory or behavioral events. Endogenous ERPs are thought to reflect the 49 neurophysiological correlates of cognitive processes. 50 In the oddball paradigm, the auditory stimuli elicited ERPs characterized by sev-51

⁵² eral components (N1, P2, N2, P3) whose latencies and amplitudes differentiated rare
⁵³ from frequent stimuli (Alexander et al., 1994; Michalewski et al., 1986; Näätänen,
⁵⁴ 1990). The N1 wave is generated by a stimulus-driven attention-trigger mechanism

(Näätänen & Picton, 1987). A positive component P2 of the ERP is often preced-

ing the negative component N2 at approximately 250 ms after rare stimuli (Goodin 56 et al., 1978). This wave may often be dissociated into an earlier fronto-central N2a 57 component (also known as "mismatch negativity") and a later, more frontally dis-58 tributed, N2b component associated with the allocation of attention to the eliciting 59 stimulus in the active oddball condition (Näätänen, 1990; Squires et al., 1975). The 60 mismatch negativity (MMN), characterized by its responsiveness to low probability 61 stimuli even in the passive auditory oddball condition, may underlie the ability to 62 discriminate acoustic differences, a fundamental aspect of sensory perception. The 63 N2 is followed by the P3 (P300) component, with larger amplitude in active than 64 in passive conditions, formed by a fronto-central wave complex N2-P3a that can 65 be dissociated from a temporo-parietal P3b wave (Molnár, 1994; Näätänen, 1990; 66 Polich, 2007; Squires et al., 1975; Verleger, 1988). In addition, at 400–500 ms from 67 stimulus onset, the rare stimuli elicited a slow frontally maximal negativity, referred 68 to as N500 (N400-like) (Gaillard, 1976). 69

Signals recorded by functional magnetic resonance imaging (fMRI) are associ-70 ated with the blood-oxygen-level-dependent (BOLD) signal, an hemodynamic indi-71 rect measure of neural activity with severe limitations in temporal resolution and 72 with challenging interpretation to make deductions about the nervous system. The 73 activation of spatially limited neuronal populations may not be strong enough to 74 produce significant hemodynamic changes, but still produce a significant ERP wave. 75 Brain imaging with fMRI has been used to localize the brain areas activated dur-76 ing the P3 wave elicited by the oddball paradigm (Linden et al., 1999; McCarthy 77 et al., 1997; Menon et al., 1997). In fMRI studies, the detection of rare stimuli in 78 oddball tasks related to BOLD signal increased in the supramarginal (Horovitz et al., 79 2002; Mangalathu-Arumana et al., 2012; McCarthy et al., 1997; Menon et al., 1997) 80 and superior temporal gyri (Mangalathu-Arumana et al., 2012; Opitz et al., 1999), 81 in agreement with greater wave amplitude of P3b observed at the temporal/parietal 82 electrode sites of EEG. A significant hemodynamic response was also reported in the 83 frontal lobe, in particular at the level of the middle frontal gyrus (MFG) (Horovitz 84 et al., 2002; McCarthy et al., 1997; Stevens et al., 2005), frontal midline areas (Menon 85 et al., 1997) an the opercular area of the inferior frontal gyrus (IFG), correspond-86 ing to Brodmann area 44 (Linden et al., 1999). The ERP response to the oddball 87 paradigm is complex and cannot be reduced to its P3 component. Besides the spatial 88 dependency of its signal on the location of blood vessels, fMRI relies on an indirect 89 correlate of neural activity which is intrinsically too slow to reveal the complexity 90 of neurodynamics. Hence, it is likely that BOLD fMRI signal generation reflects the 91 sustained activity of a large neuronal system triggered by the rare stimuli and that 92 brief synaptic activity, evoked by those stimuli in dynamic neural circuits, might be 93 detectable only with methods characterized by signal-to-response dynamics faster 94 than neurovascular signals. 95

Transcranial near infrared spectroscopy (NIRS) allows the non invasive differentiation between tissues with different light attenuation or scattering properties and a can provide spectroscopic information on the concentrations of chromophores, in particular oxy- and deoxy-haemoglobin, HbO2 and Hb (Chance et al., 1993; Delpy & Cope, 1997; Gratton et al., 1995; Scholkmann et al., 2014; Strait & Scheutz, 2014;

Torricelli et al., 2014). A slow hemodynamic signal, corresponding to cerebral blood 101 oxygenation variations, is measured as a function of near-infrared light propagation 102 through extra-cerebral and cerebral tissue. Both the optical path length and the cere-103 brospinal fluid layer affect the measurement, but the geometry of the sulci and the 104 boundary between the gray and the white matter have little effect on the detected light 105 distribution (Okada et al., 1997). The NIRS hemodynamic signal, which is similar 106 to the BOLD signal measured by fMRI, is modified by neuronal activity through 107 neurovascular coupling with latencies of several seconds. In addition to the mea-108 surement of changes in light intensity, fNIRS instruments with a frequency-domain 109 technology of measurement allow the recording of a fast optical signal with a latency 110 in the order of milliseconds (Gratton & Fabiani, 2010). This measurement, made pos-111 sible by the modulation of light sources at a high radio-frequency (e.g., 110 MHz), 112 is based on a complex function of the tissue absorption and scattering coefficients to 113 include changes in light intensity with distance, phase, and modulation depth changes 114 of intensity-modulated light and the temporal dispersion of light from an ultrashort 115 input light pulse (Gratton et al., 1997; Gratton & Fabiani, 2001; Wolf et al., 2002). 116 Neural activity can be directly detected by fast fNIRS signal through changes in the 117 scattering coefficient of the brain tissue. A change in neuronal cell volume following 118 an action potential discharge is meant to account for subtle, yet measurable, variation 119 in the scattering properties of the tissue (Lee & Kim, 2010; Steinbrink et al., 2000; 120 Villringer & Chance, 1997). Although optical imaging with fast fNIRS signals has 121 the potential for a millimeter-level of spatial resolution, it is limited to brain regions 122 located only few centimeters below the scalp (Gratton et al., 1997). 123

The two main cortical associative auditory pathways include a posterior dorsal 124 stream processing spatial ("where") information from the posterior superior tem-125 poral gyrus (STG) to the parietal cortex, and an anterior ventral stream processing 126 an object ("what") from the anterior part of STG to IFG (Ahveninen et al., 2006). 127 Both pathways send projections to the prefrontal cortex with dorsal (DLPFC) and 128 ventral (VLPFC) regions involved in different roles during the processing of audi-129 tory information with high cognitive load (Plakke & Romanski, 2016). Simultaneous 130 recording of ERP and the corresponding NIRS response has recently raised consid-131 erable interest to complement the study of the spatial distribution of cortical and 132 subcortical activation during oddball and go-nogo tasks. Source localization based 133 on the NIRS slower hemoglobin response showed significant oddball activation in 134 temporal/parietal areas (Kennan et al., 2002) with a gender effect suggesting females' 135 event-categorization process is more efficient than in males (Jausovec and Jausovec, 136 2009), and activation of MFG by tasks that require heavy cognitive processing (Jeong 137 et al., 2018). Stronger hemodynamic responses were reported in the left prefrontal 138 cortex when participants were performing an auditory oddball task under mental 139 stress (Liu et al., 2011), but the response was stronger in the right VLPFC when 140 attending to stimuli that required higher cognitive load and negatively correlated 141 with the level of state anxiety (Tseng et al., 2018). The averaging of optical responses 142 evoked by the repetition of the same stimulus allowed the analysis of event-related 143 transient optical responses based on continuous wave measurements of light intensity 144 (Kubota et al., 2008; Medvedev et al., 2008) and the development of event-related 145

optical signal (EROS) analysis by means of frequency-domain instruments, based 146 on a measurement of phase-shifts of the fast optical signal as the photons migrate 147 through the brain tissue, which is optically modified by neural activation (Gratton 148 & Fabiani, 1998). In passive detection of deviant auditory stimuli, source localiza-149 tion by EROS reported early activity co-occurring with ERP waves localized in the 150 auditory areas of STG (Rinne et al., 1999) followed by activation of VLPFC in pre-151 attentive auditory change detection (Tse et al., 2013). At a later latency, consistent 152 with P3 and frontal negativity, EROS data have shown activation in the right MFG 153 (DLPFC) by rare stimuli during an auditory oddball task (Low et al., 2006). 154

In this study, we analyzed ERPs and EROS in the frontal cortex elicited by a passive 155 two-tone auditory oddball discrimination task. The task consisted of a random stream 156 of frequent auditory tones (1000 Hz, p = 92%) or an infrequent oddball auditory tone 157 (1500 Hz, p = 8%) being played at a constant interval of 1600 ms. In this paradigm, 158 attention is directed away from the acoustic stimuli with an explicit instruction to 159 fixate on a white cross centered on a screen. Our EROS analysis was mainly based 160 on changes in the phase delay because it has the advantage of a greater sensitivity for 161 deeper locations and a greater spatial resolution than light intensity measurements 162 (Gratton & Fabiani, 2010). These results indicate that the passive auditory oddball 163 task modulated the brain activity measured by EROS in the frontal cortex within 164 the same time range as EEG measures. The simultaneous recording of fNIRS and 165 EEG measurements with high temporal accuracy over the human prefrontal cortex 166 supports the potential for this approach to unravel the functional network involved 167 in cognitive processing. 168

169 2 Methods

170 2.1 Participants

Ten healthy volunteers participated in the study (mean age = 28.1 years; 6 women).
All subjects were right-handed and reported normal hearing and normal or correctedto-normal vision. Prior to participation, subjects were informed about the procedure
and provided signed informed consent for their participation in line with the Declaration of Helsinki (World Medical Association, 2013) and the recommendations of
ethical and data security guidelines of the University of Lausanne. Two subjects (1
male and 1 female) were treated as pilot data and were excluded from the analysis.

178 2.2 Procedure

The task consisted of 12 blocks with 120 trials each, following the passive auditory oddball paradigm. Frequent (1000 Hz at occurrence probability p = 92%) and a Author Proof

rare (1500 Hz, p = 8%) computer generated tones, lasting 500 ms, were presented at approximately 60 dB SPL. Each block consisted of a randomized sequence of frequent and rare tones where stimuli onsets were separated by 1600 ms. Subjects were only instructed to watch a white fixation cross in the center of a computer screen placed horizontally at 65 cm in front of the middle of their eyes. In order to minimize the noise added by environmental light in the NIRS data, experiments were run with the lights off and the computer screen background was black.

188 2.3 Electrophysiological Recording

Continuous EEG was recorded using 64 scalp Ag/AgCl active electrodes (ActiveTwo 189 MARK II Biosemi EEG System, BioSemi B.V., Amsterdam, The Netherlands), sam-190 pled 1024 Hz and referenced to the linked mastoids. Impedance was kept below 191 20 kΩ. Electrodes were mounted on a head-cap (10/20 layout, NeuroSpec Quick 192 Cap) that was modified in order to allow the optical equipment to have direct contact 193 with the scalp (Fig. 1a). Data were preprocessed and analyzed with the EEGLAB 194 toolbox (MATLAB, The MathWorks, Inc.) (Delorme & Makeig, 2004). EEG data 195 were then segmented into epochs using markers. Epochs of the continued data with 196 visible large movement artifacts were removed from the analysis. A poor EEG signal 197 from a selected electrode was reconstructed by combining signals from neighbor-198



Fig. 1 a Schematic representation of the co-localization of the 8 light detectors (red circles) and 22 light sources (blue squares) over prefrontal and premotor areas of the cerebral cortex and the 64-channel electrophysiological setup with the standardized International 10/20 system. **b** The photo-multiplier tube detectors and fiber optic bundles placed over the participant's forehead using a custom-made mounting system

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ing electrodes using interpolation. The EEG signal was decomposed using an Infomax Independent Component Analysis (ICA) in order to correct eye blink artifacts.
Epochs containing visible artifacts after ICA preprocessing were rejected. All epochs
kept for the analysis were bandpass filtered between 0.1 and 40 Hz before ERPs were
computed.

A grand average of the ERP response to the oddball task was calculated by averag-204 ing individual participants' ERPs. In this study, we report data recorded at electrode 205 sites Fz, Cz, and Pz, separately for frequent and rare tones. The amplitude was cal-206 culated as the voltage difference between a pre-stimulus baseline and the respective 207 peak. The latency was defined by the lag for the ERP wave to reach its peak ampli-208 tude. We focused our topographic analysis on the time windows corresponding to 209 the main ERP components. The N1/P2 was identified as negative deflection between 210 120 and 150 ms post-stimulus followed by a positive deflection between 170 and 211 230 ms post-stimulus. The MMN/N2 was identified as the largest peak occurring 212 230–260 ms after stimulus presentation, the P3a as the positive deflection between 213 280 and 300 ms and the P3b as the largest peak occurring 350-400 ms after stim-214 ulus presentation. A large negative wave between 460 and 650 ms post-stimulus 215 characterized the N500 (N400-like) component of the ERP. 216

217 2.4 Optical Recording

Optical data were collected using a frequency-domain NIRS system ISS Imagent 218 (Champaign, Illinois, USA) with 8 detectors and 22 frequency-modulated light 210 (830nm wavelength modulated at 110MHz) sources. The sources and detectors 220 were co-located with the EEG setup, as shown in Fig. 1a. In the present study, EROS 221 was recorded with source-to-detector distances between 20 and 55 mm. The fiber 222 optic bundles connected to the laser diodes emitting light sources and the fiber optic 223 bundles connected to the detectors (photomultiplier tubes) were held in place using 224 a custom-built head mounting system (Fig. 1b). Detectors amplifiers' were modu-225 lated at a frequency of 110.005 MHz. Hence, a heterodyning frequency (or cross-226 correlation frequency) was generated equal to the difference between the frequency 227 modulation of the sources and detectors, i.e. 5000 Hz, thus implying a period of oscil-228 lation of 0.2 ms. The photomultiplier output current was Fast Fourier Transformed 229 (FFT) on four oscillations (i.e., 0.8 ms). One oscillation was skipped in order to avoid 230 cross-talk between sources, thereby yielding a data acquisition period of 1 ms for 231 each source. Light sources were time multiplexed in a cycle of eight per sampling 232 point, which corresponds to an effective time resolution of 8 ms (i.e., an effective 233 sampling rate 125 Hz). Notice that for each data point, we measured the DC (average) 234 intensity, AC (amplitude) intensity, and relative phase delay. 235

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The locations of each source and detector were digitized with a 3D digitizer (FAS-236 TRAK 3Space, Polhemus Inc.). Phase delay measurements in the cross-correlation 237 signal were corrected off-line for phase wrapping and their mean was adjusted to 238 zero. The algorithm described in Gratton and Corballis (1995) was used to remove the 239 pulse artifacts from the signal. Only channels with phase standard deviation smaller 240 than 200 ps were included for further analysis (Gratton et al., 2006). Data were band-241 pass filtered between 0.1 and 10 Hz before statistical topographical surface projection 242 maps of fast optical signals were computed using the Opt3D software (Gratton, 2000) 243 available at the NeuroImaging Tools & Resources Collaboratory (https://www.nitrc. 244 org/). EROS data were spatially filtered with an 8-mm Gaussian kernel and for each 245 subject, contrast, and voxels, t-scores were computed and converted to Z-scores. 246 This approach removes emphasis on larger effects in relation to the smaller effects 247 and was chosen because of our small sample size (N = 8). 248

The regions of interests (ROIs, cf. Table 1 and Fig. 2) were selected on the basis of previous studies on auditory deviance detection. The Talairach space boundaries of our ROIs were kept consistent with anatomical structures and we assigned each ROI to a Brodmann area with the BioImage Suite software package (http://www. bioimagesuite.org, Lacadie et al., 2008).

Region	Left	Right	Broadmann area
Superior frontal gyrus (SFG)	$x \in [-35, -15]$	<i>x</i> ∈ [30, 10]	BA 9/BA 8
	<i>y</i> ∈ [25, 55]	<i>y</i> ∈ [25, 55]	
	<i>z</i> ∈ [50, 35]	$z \in [50, 35]$	
Middle frontal gyrus (MFG) dorsolateral prefrontal cortex (DLPFC)	<i>x</i> ∈ [−50, −35]	<i>x</i> ∈ [45, 30]	BA 46 (/BA 10), BA 8 / BA 9
	<i>y</i> ∈ [25, 55]	$y \in [25, 55]$	
	$z \in [30, 15]$	$z \in [20, 30]$	
Inferior frontal gyrus (IFG)	$x \in [-60, -45]$	$x \in [60, 45]$	BA 44 (/BA 45)
ventrolateral prefrontal cortex (VLPFC)	<i>y</i> ∈ [15, 30]	<i>y</i> ∈ [15, 30]	-
()	$z \in [15, 30]$	$z \in [15, 30]$	
Dorsal premotor (PMd) cortex	$x \in [-40, -15]$	$x \in [35, 10]$	BA 6
	<i>y</i> ∈ [25, 55]	$y \in [25, 55]$]
	$z \in [45, 60]$	$z \in [45, 60]$	

Table 1 Coordinates (x, y, z) are in Talairach space (Talairach & Tournoux, 1988) of the areas studied here



Fig. 2 Antero-posterior (a) and left hemisphere lateral (b) views of selected regions of interest (ROIs). The area in darker grey represents the brain region sampled by the recording montage. VLPFC: ventrolateral prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; SFG: superior frontal gyrus; PMd: dorsal premotor cortex

254 **3 Results**

255 3.1 Grand Average ERPs

The sample size for the ERP analysis was N = 7 because one more subject (male) 256 was excluded due to a technical problem that occurred during EEG data collection. 257 The frequent and rare tones elicited similar negative ERP component between 120 258 and 150 ms (N1), followed by a small positive wave P2 (P180), along the midline 259 sites, somewhat larger in the rare condition and towards frontal areas (Fig. 3a, B1). 260 A second ERP peak negativity was mainly elicited in the rare tone condition at 230– 261 260 ms post-stimulus (MMN/N2) at all three midline sites (Fig. 3a). We observed 262 distinct topographic maps of electrical activity between the conditions during this 263 time window (Fig. 3B2), but it was significantly different from the frequent tone 264 ERP only on the frontal site (p < 0.05, Bonferroni-corrected for 64 electrodes). It is 265 possible that such fronto-central N2 wave is a composite of N2a and N2b components, 266 which overlap in time and scalp distribution. 267

²⁶⁸ Consistently with the literature, a significant difference between the two condi-²⁶⁹ tions (p < 0.05, Bonferroni-corrected for 64 electrodes) appeared for a large positive ²⁷⁰ deflection elicited with a lag of approximately 300–400 ms (P300) after rare tones at ²⁷¹ all reported electrode sites. This positive wave included a fronto-central component P3a (Fig. 3B3) peaking between 280 and 330 ms and a second component P3b with



Fig. 3 a Grand average ERP waveforms (mean $\pm 2 \times$ SEM) at electrode sites Fz, Cz and Pz (N = 7 participants). Each plot is followed by the result of a paired *t*-test between the frequent (dashed blue) and rare (red) tones (Bonferroni-corrected for 64 electrodes, in red when p < 0.05). **b** Topographic maps of scalp potential distribution at the main ERP components. **B1**: N1 at 120–150 ms post-stimulus; **B2**: MMN/N2 at 230–260 ms; **B3**: P3a at 280–330 ms; **B4**: P3b at 350–400 ms; **B5**: N500 (N400-like) at 475–525 ms

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a posterior maximum (Fig. 3B4), peaking between 350 and 400 ms. A large frontal
negativity observed between 450 and 600 ms (N400-like/N500) was characterized
by maximal response over midline frontal electrodes (Fig. 3B5).

275 **3.2 EROS**

The data acquisition problem encountered during EEG recording of one participant did not affect fNIRS, therefore the sample size for the EROS analysis was N =8. The spatiotemporal profile of the optical signal response corresponded to the topographical maps on group-level *Z* statistics of a 'differential EROS response', which resulted from the contrasts conducted within the ROIs for each condition separately relative to pre-stimulus baseline and for rare versus frequent tones, to the three time points of the peak contrasts, i.e. at 40, 256, and 480 ms (Fig. 4).

Rare tones elicited less bilateral activation compared to frequent tones between 283 32 and 40 ms following the stimulus onset (Fig. 4A). In the left hemisphere, the 284 negative peak voxel activity was located in the Brodmann Area BA46 (DLPFC, 285 ROI in blue in Fig.2, Talairach coordinates x = -43, y = 27) and did not reach 286 (Z = -2.135) the level of significance (p = 0.05) when averaging the voxels within 287 the ROI ($Z_{\text{crit}(0.05)} = -2.60$). The right negative peak voxel activity belonged to the 288 posterior part of BA8 (x = 24, y = 27) across superior frontal gyrus (ROI in green in 289 Fig. 2) and did not reach the ROI significance criterion ($Z = -2.169 > Z_{crit(0.05)} =$ 290 -2.85). 291

At 256 ms post-stimulus, Fig. 4b shows the statistical maps resulting from dif-202 ferential EROS responses and Fig. 5 shows also the responses in the rare and fre-293 quent tone conditions, representing a complex pattern of activity co-occurring with 294 N2 component of the ERP. Between 240 and 272 ms in the rare tone condition, 295 we observed greater activation (Z > 2) in the ROI corresponding to the left PMd 296 (ROI in red in Fig. 2, x = -21, y = 12, BA6) with a peak voxel activity at 256 ms 297 $(Z = 2.263 < Z_{crit(0.05)} = 2.67)$. Between 240 and 264 ms, we observed a reduced 298 differential EROS response in the right SFG (BA8, x = 24, y = 29) with a peak 299 voxel activity at 256 ms ($Z = -2.368 > Z_{crit(0.05)} = -2.89$). Those two effects were 300 very close to their ROI criterion of significance at p = 0.05. 301

Broca's area (VLPFC, ROI in yellow in Fig. 2, y = 22, z = 22), correspond-302 ing to BA44 contained and limited by pars opercularis of the left inferior frontal 303 gyrus, was characterized by a greater activation in the rare tone condition in the 304 interval 248–264 ms with a significant peak voxel activity at 264 ms (Z = 2.234305 > $Z_{crit(0.05)} = 2.20$). This ROI was activated almost exclusively during the rare 306 tone condition, as emphasized by the significant contrast (maximum at 272 ms, 307 $Z = 2.245 > Z_{crit(0.05)} = 2.19$) of this condition with the baseline between 248 and 308 280 ms (Fig. 5b, sagittal projection). In the left hemisphere, it is interesting to notice 309 also an activation at the level of the auditory cortex in the postcentral gyrus (BA 43) 310 only after frequent tones (Fig. 5c). This activation fell below a significant contrast 311 (Z < 2) and was not visible in the differential EROS response (Fig. 5a). 312



Fig. 4 Spatial maps based on group-level (N = 8) Z statistics for the EROS data contrasting rare versus frequent tones in the passive auditory oddball task relative to the pre-stimulus baseline. The area in light grey represents the brain region sampled by the recording montage. **a** Projection of EROS data to the axial surface at 40 ms after stimulus onset. The differential EROS response shows that superior frontal gyrus was activated after frequent tones by the dorsal spatial ("where") processing stream, BA46 in the left hemisphere and BA8 in the right hemisphere. **b** Spatial maps of the EROS data projected to the axial (top) and left sagittal (bottom) surfaces of significant ROIs at 256 ms after stimulus onset, co-occurring with N2b ERP wave. Notice the complex pattern of response, see Fig.5 for more details. **c** Projection to the axial (top) and right sagittal (bottom) surfaces of significant ROIs at 480 ms after stimulus onset, co-occurring with N500 (N400-like) ERP wave. In the right hemisphere, notice the strong activation of DLPFC after rare tones at the level of BA9 (axial projection) and BA46 (sagittal projection)

In the right middle frontal gyrus (Fig. 4C), at the level of BA9 of DLPFC (Talairach coordinates x = 32, y = 39), a greater activation was observed between 464 and 520 ms in the rare tone condition with a peak voxel activity at 488 ms ($Z = 2.361 < Z_{crit(0.05)} = 2.97$). This activation co-occurred with the N500 (N400-like) ERP wave. A more anterior part of DLPFC, corresponding to BA46 (see the right hemisphere sagittal view of Fig. 4c), was also activated by the differential EROS response during this interval, but it was located outside the predefined ROIs.

320 4 Discussion

We report results on the neural dynamics of frontal cortex response to a passive auditory oddball task studied by simultaneous recording of fast optical signals with high temporal resolution (EROS) and ERPs. To the best of our knowledge, no other Event-Related Potentials and Fast Optical Imaging ...



Fig. 5 Spatial maps based on group-level (N = 8) Z statistics for the EROS data at 256 ms after tone onset, co-occurring with N2b ERP wave, projected to the axial (top) and left sagittal (bottom) surfaces. **a** Response contrasting rare versus frequent tones compared to pre-stimulus baseline, same as Fig. 4b. **b** Response to rare tones separately contrasted with pre-stimulus baseline. Notice the same ROIs visible in panel (**a**), although with a different significant voxel density. **c** Response to frequent tones contrasted with pre-stimulus baseline. Notice a small activation in the postcentral gyrus, at the border of the area under investigation

study has yet combined EROS with a similar temporal resolution (i.e. 8 ms sampling 324 time) with a 64-channel EEG system in an auditory oddball task. Electrophysiological 325 recordings revealed all the ERP components (N1, P2, N2, P3) well described in the 326 literature (Alexander et al., 1994; Michalewski et al., 1986; Näätänen, 1990). We 327 observed also several commonalities and some differences regarding the brain areas 328 and the response timing with the few previous studies reporting EROS analyses in 329 auditory and visual oddball tasks (Low et al., 2006; Proulx et al., 2018; Tse & Penney, 330 2008; Tse et al., 2006, 2013). Despite controversial observation about the significance 331 of fast optical signals measured by fNIRS (Steinbrink et al., 2005; Syré et al., 2003), 332 the co-occurrence of optical signals and ERP waves found here confirms that such 333 a methodological approach carries the potential for investigating neurodynamics of 334 cognitive activity in a wide range of tasks (Gratton et al., 2018). However, there 335 are several limitations that should be acknowledged in our results. First, this study 336 may be considered somewhat preliminary because of the small sample size (N = 7)337 for ERP and N = 8 for EROS analyses), although the statistical analyses showed 338 suitable effects. Additional data are being collected and a final report with a larger 339 sample will be soon completed. Second, fast optical signals suffer from a low signal-340 to-noise ratio and the response signal is limited to a few centimeters below the scalp 341 (Gratton & Fabiani, 2010). It is important to underline that complementary studies 342 using different and independent measures of brain activity are necessary to gain 343

further insights of the spatiotemporal patterns of brain dynamics while performing
 behavioral tasks.

After the stimulus onset, the earliest response observed in this study is an optical 346 signal in the differential EROS response, appeared as early as between 32 and 40 ms 347 post-stimulus showing a bilateral activation that is larger for frequent than rare stim-348 uli, thus suggesting a short latency input from the auditory system. The localization 340 of the signal at the level of BA46 of DLPFC in the left hemisphere and at the level 350 of BA8 of the superior frontal gyrus in the right hemisphere suggests that the input 351 is not from the sensory ascending subcortical pathway. The DLPFC is the end point 352 for the dorsal stream that transmits spatial ("where") information (Ahveninen et al., 353 2006; Plakke & Romanski, 2016). 354

The next evoked activity response was an ERP component with a negative peak 355 observed along the midline, mainly fronto-central sites, between 120 and 150 ms 356 post-stimulus followed by a smaller positive wave. The profile and the latency of this 357 wave was similar after frequent and rare tones, although the amplitude after rare tones 358 tended to be larger. The latency and localization of this peak is in agreement with 359 the N1/P2 (N100-P200) complex reported for the auditory oddball task with strong 360 generators in the auditory areas of the STG and with association with a stimulus-361 driven attention-trigger mechanism (Näätänen & Picton, 1987; Rinne et al., 1999). 362 In previous imaging studies coupled with EEG, the N100 component during auditory 363 tasks co-occurred also with a signal in the anterior cingulate cortex (ACC) (Esposito 364 et al., 2009; Walz et al., 2013). At this latency, we could not observe any significant 365 optical response in our ROIs of the prefrontal cortex. This is likely due to the fact 366 that our fNIRS montage was not designed to record neither from the auditory cortex 367 nor from ACC. 368

The typical event-related response to the stimulus presentation observed in the 369 auditory oddball task is the N2/P3 (P300) wave complex (Alexander et al., 1994; 370 Fabiani & Friedman, 1995; Näätänen & Picton, 1987; Squires et al., 1975). This 371 wave is characterized by several components, which may overlap in time and scalp 372 distribution. We observed a fronto-central N2b-P3a component (Fig. 3B2 and B3) 373 between 230 and 330 ms post-stimulus, followed by a P3b component with a parietal 374 maximum (Fig. 3B4), peaking between 350 and 400 ms. Source locations determined 375 from fMRI showed that the ACC was the principal generator of N2b-P3a ERP wave 376 following dipole modeling of ERPs (Crottaz-Herbette & Menon, 2006). We observed 377 fast optical signals correlated with the timing of this wave, but their latency was 378 different (up to approximately 100 ms later) than the lag reported from other oddball-379 related EROS analyses (Low et al., 2006, 2009; Proulx et al., 2018; Tse et al., 2006, 380 2013; Tse & Penney, 2008). Differences in the protocol of our passive oddball task 381 with respect to previous studies might explain differences in the temporal profile 382 of the response. The current occurrence probability of rare (i.e., deviant) stimuli 383 was p = 8% compared to p = 20% (Low et al., 2006, 2009; Proulx et al., 2018), 384 which could suggest that in our protocol rare tones were likely to be much more 385 unattended. The duration of our tones was 500 ms, that was much longer than usual 386 stimuli duration in oddball studies, i.e. 70–100 ms (Ruusuvirta et al., 2007; Tse & 387 Penney, 2008; Tse et al., 2006, 2013), and longer than 400 ms used in similar EROS 388

settings (Baniqued et al., 2013; Low et al., 2006, 2009). Moreover, we 1500 Hz instead 500 Hz for the rare tone frequency pip and 60 dB SPL instead of 70 db SPL for the loudness (Low et al., 2006, 2009; Proulx et al., 2018). Hence, our 391 protocol might have triggered a different dynamics or slightly different processes 392 that we observed in our EROS analysis. Filtering parameters are very important for 393 the detection of fast optical signals with a low signal-to-noise ratio (Maclin et al., 304 2003). In this study EROS was bandpass filtered in the range 0.1–10 Hz, compared 395 to 0-5 Hz (Low et al., 2006, 2009), 0.5-10 Hz (Baniqued et al., 2013), 1-10/12 Hz 396 (Tse & Penney, 2008; Tse et al., 2006, 2013), and 2-20 Hz (Proulx et al., 2018) of 397 the other studies. 398

The differential EROS response occurring at the same time of the N2/P3 ERP 399 showed an activation in the inferior frontal gyrus at the level of left PMd (BA6) for 400 the rare tones. Both action control and action observation require premotor functions 401 and left PMd participates to mapping external action parameters onto the appropriate 402 motor repertoire (Moisa et al., 2012; Stadler et al., 2012). In addition to the premotor 403 functions, our finding supports the hypothesis that the activation of the left PMd 404 may reflect encoding of the semantic features of actions (i.e., cognitive aspects of 405 the sensorimotor sequences associated with the detection of deviant stimuli) (Press 406 et al., 2012). Around at the same time, a pattern of activation opposite to this one 407 for PMd was observed for EROS in the superior frontal gyrus at the level of BA8, 408 near the border of BA46 in the DLPFC. This area was slightly activated by frequent 409 tones, but it was strongly deactivated by rare tones compared to baseline activity. 410 This signal was not observed by Low et al. (2006), but in their study rare tones were 411 less unattended (20% of the total number of stimuli vs. 8% in our protocol). BA46 is 412 mostly related with the executive control of language production (Ardila et al., 2016) 413 and we suggest that the source of the observed signal was rather BA8. This area of 414 right DLPFC is involved in pitch and memory processing of the auditory stimulus 415 (Kumar et al., 2015; Schaal et al., 2017). Hence, our results might suggest that in the 416 passive oddball task this part of BA8 would be more active when a retrieval attempt 417 of the frequent tone succeeded than when it failed. 418

We observed an optical signal in the left VLPFC (BA44, Broca's area) occurring 419 with N2 ERP component, in agreement with previous studies (Linden et al., 1999; 420 Medvedev et al., 2010; Tse et al., 2006). The activation in BA44 was strong after 421 rare tones and occurred about at the same time of a lesser activated area in the left 422 postcentral gyrus (BA43) after frequent tones. The anterior ventral stream that brings 423 information about the stimuli's characteristics (i.e., processing an object "what" 424 information) projects to VLPFC (Ahveninen et al., 2006; Plakke & Romanski, 2016). 425 Broca's area (BA44 in the left VLPFC) is involved in semantic tasks, in the motor 426 aspect of speech, and in music perception (Bezgin et al., 2014; Flinker et al., 2015; 427 Levitin & Tirovolas, 2009). The activation of BA43 and surrounding areas in STG 428 was reported for abstract auditory representations and mental imagery of speech 429 (Chiang et al., 2013; Tian et al., 2016). The differential spatial pattern of response 430 observed in our results, between BA44 and BA43, might suggest that the oddball 431 task could engage inhibitory processes triggered by deviant stimuli, as suggested in 432 the literature in association with theta band oscillations (Harper et al., 2014; Jonides 433

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et al., 1998; Proulx et al., 2018). We did not analyze here these oscillations, but this is certainly an interesting analysis to be developed in our extended experiment and future studies.

Previous studies have shown ERP negative waves at a latency between 300 and 500 437 ms post-stimulus elicited in target detection and oddball tasks (Codispoti et al., 2006; 438 Kiehl et al., 2006; Low et al., 2006; Stevens et al., 2005), which was observed in our 430 results as a large N500 (N400-like) wave. Our ERP analysis showed that N500 was 440 almost exclusively elicited by rare tones and its amplitude was much larger for Fz, in 441 agreement with the frontal and right hemisphere topographical distribution reported 442 in those previous studies. The N400-like component has been usually reported with 443 a spatial distribution over centro-parietal or centro-posterior sites in lexical decision 444 tasks and in relation to predictability of stimuli and in the inferior frontal regions, 445 if the effect reflected integration difficulty (Kutas & Hillyard, 1984; Kutas & Fed-446 ermeier, 2000; Lau et al., 2008; Rossi et al., 2013). Our EROS analysis showed an 447 activation at the level of DLPFC, more specifically in the right hemisphere for two 448 close regions across the Brodmann areas BA9 and BA46. Neuroimaging analysis by 449 fMRI reported that the DLPFC corresponding to the areas BA9/BA46 in the right 450 middle frontal gyrus was involved in maintaining integrated information (Collette 451 et al., 2005; Prabhakaran et al., 2000), associated with the acquisition of abstract 452 rules (Monte-Ordoño & Toro, 2017; Sun et al., 2012) and accompanying conscious 453 experience of abstract auditory percepts (Brancucci et al., 2016). 454

455 **5** Conclusion

The data of the current study demonstrate that cognitive neural dynamics or pre-456 frontal cortical activity during a passive auditory oddball task can be studied by a 457 non-invasive fast optical imaging technique (EROS) with co-localized EEG mea-458 surements. We identified significant co-occurrences of EROS and ERP responses to 459 rare tones. By combining high spatial and temporal resolution we observed that left 460 and right pre-frontal structures were differentially affected. The left dorsal premo-461 tor cortex and Broca's area in the left VLPFC were activated by rare tones during 462 the mismatch negativity and N2 ERP components, whereas frequent tones activated 463 a small area in the right superior frontal gyrus involved in memory processing of 464 the auditory stimulus. Moreover, our results showed a significant N500 (N400-like) 465 wave associated with the activity of DLPFC after rare tones, likely related with the 466 maintenance of integrated information. 467

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