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1 **Empirical Bayes evaluation of fused EEG-MEG source reconstruction:**
2 **Application to auditory mismatch evoked responses**

3

4 Françoise Lecaigard^{1,2*}, Olivier Bertrand^{1,2}, Anne Caclin^{1,2**}, Jérémie Mattout^{1,2**}

5

6 ¹ Lyon Neuroscience Research Center, CRNL; INSERM, U1028; CNRS, UMR5292;
7 Brain Dynamics and Cognition Team, Lyon, F-69000, France

8 ² University Lyon 1, Lyon, F-69000, France

9

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11 * Corresponding author

12 ** Both authors equally contributed to this work.

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14

15 **Correspondence:**

16 Françoise Lecaigard
17 INSERM U1028 - CNRS UMR5292
18 Centre de Recherche en Neurosciences de Lyon
19 Equipe DYCOG
20 Centre Hospitalier Le Vinatier (Bât. 452)
21 95, Boulevard Pinel
22 69500 Bron, France
23 francoise.lecaigard@inserm.fr

24

25 **Telephone:** 0033 472138963

26 **Fax:** 0033 472138901

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30 **Keywords:** EEG and MEG source reconstruction

31 Data fusion

32 Bayesian model comparison

33 Group-level inference

34 Mismatch Negativity (MMN)

35 Early Deviance Response

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38 **Highlights**

- 39 • Empirical evaluation of EEG-MEG source inversion is achieved in a
40 Bayesian framework
- 41 • Multimodal information yields both a better fit and a reduced model
42 complexity
- 43 • MEG was found more informative than EEG for auditory responses
- 44 • EEG proved useful to disambiguate between alternative spatial cortical
45 models
- 46 • A highly precise spatio-temporal description of auditory generators was
47 thus obtained

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49

50 **Abstract**

51

52 We here turn the general and theoretical question of the complementarity of EEG
53 and MEG for source reconstruction, into a practical empirical one. Precisely, we
54 address the challenge of evaluating multimodal data fusion on real data. For this
55 purpose, we build on the flexibility of Parametric Empirical Bayes, namely for EEG-
56 MEG data fusion, group level inference and formal hypothesis testing.

57 The proposed approach follows a two-step procedure by first using unimodal or
58 multimodal inference to derive a cortical solution at the group level; and second by
59 using this solution as a prior model for single subject level inference based on either
60 unimodal or multimodal data. Interestingly, for inference based on the same data
61 (EEG, MEG or both), one can then formally compare, as alternative hypotheses, the
62 relative plausibility of the two unimodal and the multimodal group priors. Using
63 auditory data, we show that this approach enables to draw important conclusions,
64 namely on (i) the superiority of multimodal inference, (ii) the greater spatial sensitivity
65 of MEG compared to EEG, (iii) the ability of EEG data alone to source reconstruct
66 temporal lobe activity; (iv) the usefulness of EEG to improve MEG based source
67 reconstruction.

68 Importantly, we largely reproduce those findings over two different experimental
69 conditions. We here focused on *Mismatch Negativity* (MMN) responses for which
70 generators have been extensively investigated with little homogeneity in the reported
71 results. Our multimodal inference at the group level revealed spatio-temporal activity

72 within the supratemporal plane with a precision which, to our knowledge, has never
73 been achieved before with non-invasive recordings.

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75 **Introduction**

77 Source reconstruction of electrophysiological responses have become a standard
78 analysis in neuroimaging, as revealed by the increasing number of papers using such
79 techniques, as well as the numerous methodologies afforded by electrophysiological
80 analysis software. Whatever the methodology (Lecaignard and Mattout, 2015), the ill-
81 posed nature of the underlying inverse problem remains (from a mathematical point
82 of view, recognition of true generators is impossible). This issue calls for data
83 carrying enough information about the underlying cortical generators, as it is more
84 likely the case when bringing together EEG and MEG recordings as proposed more
85 than 30 years ago (Cohen and Cuffin, 1987; Puce and Hämäläinen, 2017). This
86 paper addresses the added value of combining EEG and MEG data for distributed
87 source localization, which we evaluated here *empirically* with auditory mismatch
88 responses.

89

90 Merging EEG and MEG aims at accounting for information missed by one modality
91 and captured by the other one (Dale and Sereno, 1993; Fuchs et al., 1998), and
92 crucially, at reducing the under-determined nature of the ill-posed inverse problem
93 thanks to complementary information gathered by these two modalities (Plonsey and
94 Heppner, 1967). Fused reconstruction therefore appears promising to reach high
95 temporal and spatial resolutions in brain function imaging. Greater performances for
96 fusion than separate EEG or MEG source reconstructions were indeed consistently
97 reported in simulation-based studies. Quantitative evaluations rested on various
98 metrics obtained from the comparison of the true distribution (that has generated the
99 synthetic data) and reconstructed ones. In short, reduced localization errors could be
100 reported for both superficial and deep sources (Fuchs et al., 1998), as well as for
101 different signal-to-noise ratio (SNR) and sensor montages (Babiloni et al., 2004).
102 Decrease of the undesirable sensitivity of inversion methods to source orientation
103 (Baillet et al., 1999) was also reported. Further evaluation with empirical data is a
104 necessary step, but in this case the lack of knowledge of the true cortical generators
105 obviously prevents from using simulation-based metrics. To date, only few studies

106 attempted to circumvent this issue. Enhanced precision of source estimates was
107 found with visual evoked responses (Henson et al., 2009). Other studies considered
108 specific cases for which fMRI results (Sharon et al., 2007), widely described median
109 nerve stimulation (Molins et al., 2008) or intracranial recordings with epileptic patients
110 (Chowdhury et al., 2015) were assumed to provide the to-be-compared cortical
111 source distribution. All these studies were in favor of reduced errors of localization
112 with fused inversion.

113 In contrast to those approaches, a procedure for the multi-data integration was
114 proposed by Henson and collaborators (2011) that enables the empirical assessment
115 of multimodal inference. It followed a series of work, some of which we performed
116 together, to demonstrate the flexibility and usefulness of Parametric Empirical Bayes
117 (PEB) for solving the EEG or MEG inverse problem, incorporating several
118 uninformed or informed (e.g. fMRI) priors, enabling the formal comparison of
119 alternative prior models (Daunizeau et al., 2005; Friston et al., 2008b; 2006a; Henson
120 et al., 2010; Mattout et al., 2005; 2006; Phillips et al., 2005), and for EEG and MEG
121 simultaneous source reconstruction (Henson et al., 2009; 2011). This approach is the
122 one implemented in the SPM software for EEG and MEG source reconstruction. In
123 their approach, Henson and collaborators used the possibility to enforce (through
124 strong priors) the precision (confidence) associated with each modality. Hence by
125 accounting for both EEG and MEG data, or by switching off the influence of one or
126 the other, they could empirically demonstrate the superiority of the fusion approach.
127 Precisely, they report larger evidence for the fusion model (equal contribution of EEG
128 and MEG), which translates into a larger accuracy (data fit) and a lower complexity
129 (overfitting).

130
131 In the present study, we further exploits PEB and Bayesian Model Comparison
132 (Penny et al., 2010) to illustrate a slightly different approach for the empirical
133 assessment of the usefulness of EEG-MEG data fusion. We also extend the
134 demonstration of such an empirical assessment to another dataset pertaining to two
135 auditory oddball tasks. Our approach rests on model inversion for multiple subjects,
136 that is constrained by a soft group spatial prior to guide individual source
137 reconstruction. Importantly, beyond demonstrating the superiority of multimodal
138 inference, it enables to address questions such as: “can EEG, MEG or fused data
139 equally distinguish between close plausible inverse solutions?”. In other words, the

140 alternative approach illustrated here speaks to source model separability afforded by
141 each modality. Interestingly, the obtained results provide some insights onto why the
142 different modalities show different performance.

143

144 We applied the proposed evaluation scheme to auditory mismatch (or deviance)
145 responses elicited by a change (or deviant) in a regular acoustic environment,
146 including the well-known Mismatch Negativity (MMN) (Näätänen et al., 2007). This
147 choice was motivated by the outstanding place the MMN has occupied in cognitive
148 and clinical neuroscience (Auzztulewicz and Friston, 2016; Morlet and Fischer,
149 2014; Sussman and Shafer, 2014), contrasting with the arguably poor consistency of
150 findings in the MMN source research (Fulham et al., 2014; Schönwiesner et al.,
151 2007). Beside, recent findings of earlier mismatch responses than the MMN (Escera
152 et al., 2014; Lecaiguard et al., 2015) encourage to develop a comprehensive analysis
153 of auditory responses to improve our understanding of auditory (deviance)
154 processing. To date, only a few MEG studies addressed the localization of early
155 deviance components (Recasens et al., 2014a; 2014b; Ruhnau et al., 2013), with
156 activity circumscribed in the primary auditory cortex. Taken together, these recent
157 findings indicate that it is time to combine high temporal and spatial information for an
158 in-depth characterization of auditory deviance processing.

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160 Strong efforts using different neuroimaging techniques have been made to identify
161 the cortical generators of the MMN for about three decades. Functional Magnetic
162 Resonance Imaging (fMRI) and electrophysiological techniques (EEG, MEG) were
163 mostly employed, that favored spatial or temporal precision respectively. To our
164 knowledge no study has been conducted using fused inversion (simultaneous
165 recordings but separate source modeling were conducted in Huotilainen et al., 1998;
166 Kuuluvainen et al., 2014; Rinne et al., 2000). Taken together, fMRI (see for review
167 Deouell, 2007) and electrophysiological studies (Fulham et al., 2014; Giard et al.,
168 1995; Lappe et al., 2013a; Marco-Pallarés et al., 2005; Recasens et al., 2014b;
169 Ruhnau et al., 2013; Waberski et al., 2001) suggested that the most prominent
170 sources are located in temporal and frontal areas. However, there is a large and
171 acknowledged variability across findings (Deouell, 2007), obtained with various
172 experimental designs (including different physical properties of stimuli), that prevents
173 from a reliable and detailed description of the MMN network. It is possible that none

174 of these modalities may be sufficiently informed spatially and temporally when
175 employed alone, which pleads for advanced methods such as fused reconstruction.

176

177 In this context, the aim of the current study was twofold: first, to propose a general
178 method to evaluate finely and quantitatively the performance of multimodal and
179 unimodal source reconstruction with empirical data. The second aim was to provide a
180 detailed description of early and late auditory mismatch generators using advanced
181 statistical methods including fused inversion (Henson et al., 2009). We considered
182 data originating from a previous passive auditory oddball study (Lecaigard et al.,
183 2015) with two deviance features (frequency and intensity, separately manipulated)
184 and conducted with simultaneous EEG and MEG recordings. Our results
185 demonstrate the larger source model separability of fused inversion and the great
186 potential of such information integration that here produced a fine-grained description
187 of a fronto-temporal network underlying auditory processing.

188

189

190 **1. Material and Methods**

191

192 We here briefly describe the source localization methodology employed in the
193 present study including model inversion with group-level inference (Litvak and Friston,
194 2008) and EEG-MEG fusion (Henson et al., 2009). We then present our approach for
195 the quantitative evaluation of EEG, MEG and fused EEG-MEG inversion, and the
196 multimodal dataset used to validate our approach, resting on simultaneous EEG-
197 MEG recordings of auditory frequency (FRQ) and intensity (INT) deviance
198 responses.

199

200 **1.1. Methods for source reconstruction**

201

202 **1.1.1. *Forward model computation.***

203 For both MEG and EEG modalities, a three-layer realistic Boundary Element Model
204 (BEM) (Hämäläinen and Sarvas, 1989) was employed, with homogenous and
205 isotropic conductivities within each layer set to 0.33, 0.0041 and 0.33 S/m for the
206 scalp, skull and brain, respectively (Rush and Driscoll, 1968). The source domain
207 included $N_s=20484$ sources (mean average distance = 3.4 mm) distributed on the

208 cortical mesh (grey-white matter interface) and we used surface normal constraints
 209 for dipole orientation. All meshes derived from canonical uniformly tessellated
 210 templates (provided with SPM8) that had been warped from individual MRI to
 211 account for subject-specific anatomy (Mattout et al., 2007). Coregistration of the
 212 resulting head model and functional data (EEG, MEG) was achieved for both
 213 modalities separately using each time a rigid spatial transformation based on three
 214 anatomical fiducials (nasion, left and right pre-auricular points) whose positions were
 215 measured relative to sensor ones for each modality (EEG: 3D digitization using a
 216 Fastrak Polhemus system, Colchester, VT, USA; MEG: monitoring head localization
 217 coils mounted on subject’s head). For MEG data, head position was averaged across
 218 experimental sessions to allow for a common forward model between conditions. For
 219 each participant and each modality, computation of accurate BEM was performed
 220 with the software Openmeeg (<http://openmeeg.github.io>) (Gramfort et al., 2010). Re-
 221 referencing to the average mastoids was applied to EEG BEM. The resulting lead-
 222 field operator or gain-matrix $L \in \mathbb{R}^{N_c \times N_s}$ (with N_c sensors and N_s sources) embodying
 223 the pre-cited anatomical and biophysical assumptions, enters the following linear
 224 generative model M of data $Y \in \mathbb{R}^{N_c \times N_t}$ (with N_t time samples):

$$Y = LJ + \varepsilon_n \quad (1)$$

226
 227 where J represents the source distribution, i.e. the magnitude of dipole at each node
 228 of the cortical mesh, and ε_n represents the residual error term.

230 1.1.2. *Model inversion using Multiple Sparse Priors (MSP).*

231 Within a hierarchical Bayesian framework, we defined J as a multivariate Gaussian
 232 distribution of the form $J \sim \mathcal{N}(0, C_s)$ with $C_s \in \mathbb{R}^{N_s \times N_s}$ the (unknown) spatial source
 233 covariance. We assumed a multivariate Gaussian error term $\varepsilon_n \sim \mathcal{N}(0, C_n)$ with
 234 $C_n \in \mathbb{R}^{N_m \times N_m}$ the (unknown) spatial noise covariance (relatively to a normalized
 235 spatial space composed of N_m modes that will be defined in the following section).
 236 We used Multiple Sparse Priors (Friston et al., 2008b) to estimate both the
 237 distribution J that satisfies the general equation of linear model with Gaussian errors:

$$\tilde{J} = C_s L^t (C_n + LC_s L^t)^{-1} Y \quad (2)$$

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and the posterior distribution of C_s and C_n . As described in Friston et al. (2008b), C_s is defined as a linear combination of N_p variance components $Q_s^i \in \mathbb{R}^{N_s \times N_s}$ corresponding to the sparse priors weighted by hyperparameters λ_s^i :

$$C_s = \sum_{i=1}^{N_p} \lambda_s^i Q_s^i \quad (3)$$

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For the initial condition, we used SPM8 default sparse priors including 256 components in each hemisphere, and enabled inter-hemispherical coupling for each component leading to a total of $N_p = 712$ variance components. Estimation of the associated hyperparameters $\{\lambda_s^i\}_{i=1:N_p}$ was driven by the principle of source sparsity implemented in the Greedy-Search (GS) algorithm (Friston et al., 2008a). It should be noted that preliminary work (data not shown) using a various number of initial components did not reveal any significant change in the final outcome, which we attributed to the effectiveness of the sparsity constraint. At the sensor level, we assumed a single variance component equal to the identity matrix per modality and expressed in a normalized space (Henson et al., 2009) with hyperparameter weighting as follows:

$$\begin{cases} C_n = \lambda_e Q_e & \text{for EEG inversion} \\ C_n = \lambda_m Q_m & \text{for MEG inversion} \\ C_n = \lambda_e Q_e + \lambda_m Q_m & \text{for fused inversion} \end{cases} \quad (4)$$

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In the case of fused inversion, matrices Q_e and Q_m are of same size (each having non-null modality-specific elements in separate part of the matrix to enable their concatenation in matrix C_n). MSP rests upon expectation maximization (EM) and provides Restricted Maximum Likelihood (ReML) estimates of hyperparameters $\lambda = \{\lambda_s^1, \dots, \lambda_s^{N_p}; \lambda_{modality}\}$, Maximum A Priori (MAP) estimate of J (Friston et al., 2007) and the free energy \mathcal{F} , an approximation of the posterior log-evidence of the model (the log-value of $p(Y|M)$, the probability of observing the data Y given the generative model M defined in Eq.(1); further details are provided in Appendix).

267 1.1.3. *Group-level inference.*

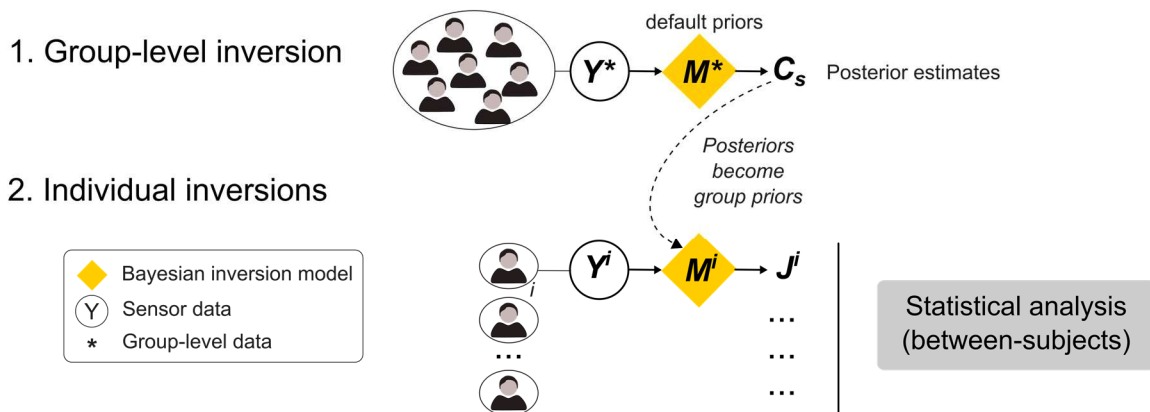
268 Group-level inference (Litvak and Friston, 2008) aims at specifying the prior
269 distribution on the source covariance C_s by accounting for the assumption that
270 distribution J should be common to all participants. This is a two-step procedure
271 (Figure 1.A) that we used in the present reconstruction study (using SPM8) and that
272 has also inspired our quantitative evaluation of fused inversion (see below):

- 273 • In the first step we perform a single *group-level* inversion using default sparse
274 priors. Resulting posterior hyperparameters are thus informed by the group-
275 level variance of the data; they provide a posterior on C_s (Eq.(3)).
- 276 • In the second step we proceed to *individual-level* inversions, starting with the
277 group-informed posterior on C_s as prior, here referred to as *group priors*.

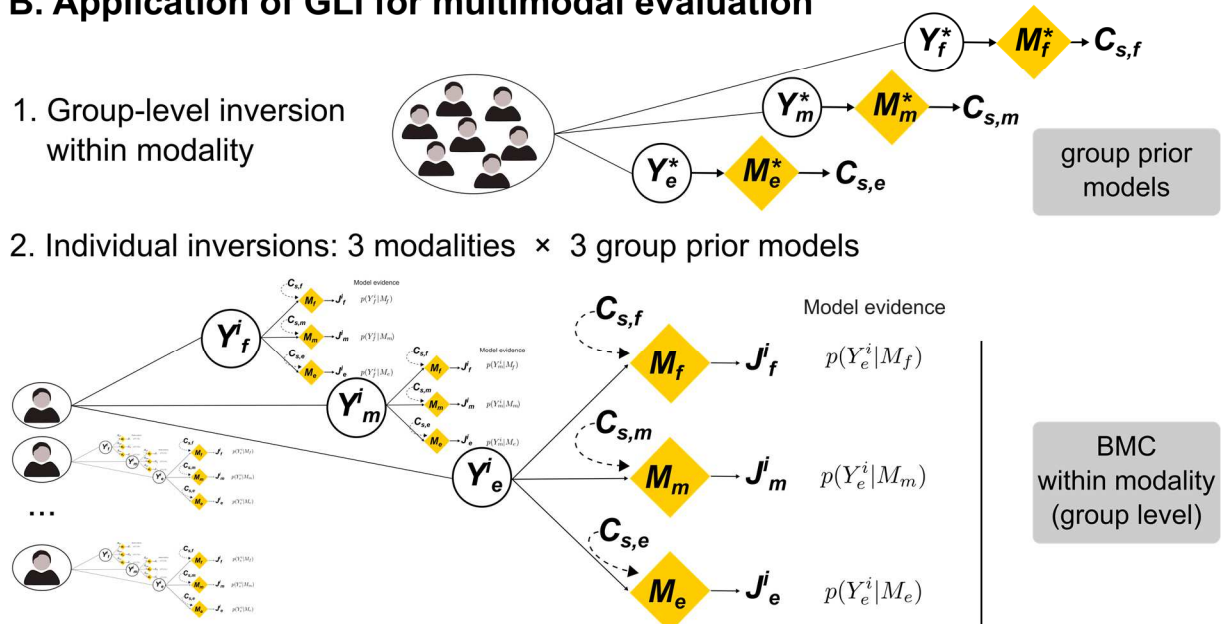
278 In practice, as detailed in Litvak and Friston (2008), the second step is left with two
279 hyperparameters to estimate in the case of unimodal inversion ($\{\lambda_s; \lambda_e\}$ and $\{\lambda_s; \lambda_m\}$
280 for EEG and MEG inversions, respectively) and three terms in the case of fused
281 inversion ($\{\lambda_s; \lambda_e, \lambda_m\}$). Prior to data inversion, group-level inference involves the
282 normalization of the individual sensor-level data in a common spatial-mode space
283 (Friston et al., 2008b). In short, this space is composed of N_m orthogonal virtual
284 sensors (referred to as spatial modes) resulting from the singular value
285 decomposition (SVD) of a group-informed gain matrix. Data reduction is also
286 achieved using a subsequent projection of the data on temporal modes (Friston et al.,
287 2006b). For each subject, the spatially and temporally projected data $\tilde{Y}_i \in \mathbb{R}^{N_m \times N_t}$ is
288 rescaled (using the trace of $\tilde{Y}_i \tilde{Y}_i^t$) to accommodate signal amplitude differences over
289 spatial modes. After model inversion, the reconstructed source activity J is projected
290 on spatial modes and the percentage of data explained by J is computed to quantify
291 the variance explained by J relative to the residual variance.

292

A. Group-Level Inference (GLI)



B. Application of GLI for multimodal evaluation



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294

295 **Figure 1. Procedure for multimodal evaluation. A. Schematic view of group-**

296 **level inference** (Litvak and Friston, 2008). The two-stage procedure aims at

297 *constraining subject-specific inversion with empirical source priors reflecting cortical*

298 *activity common to the group. Notations Y , M , C_s and J refer to sensor data, inversion*

299 *model, source covariance and source distribution respectively, as specified in the*

300 *main text. Mean distribution results from between-subjects statistical analysis. B.*

301 **Evaluation scheme.** The three separate group-level inversions performed for each

302 *modality provides the source priors for subsequent subject-specific inversions (nine*

303 *per subject). After individual inversions, within each modality, Bayesian model*

304 *comparison (BMC) proceeds at the group level using approximated model evidence*

305 *to select which models (M_e , M_m or M_f) performs best. In this panel, model notation*

306 *(M) is related to the modality of group priors only (subject superscript has been*

307 *removed although inversion model is subject-specific) to highlight the fact that for*

308 *each subject, the three competing models only differ with this respect.*

309

310

311 1.1.4. *Fused EEG-MEG inversion.*

312 The fused inversion approach proposed in Henson et al. (2009) was employed in the
313 current study. This method entails the necessary rescaling of data and gain matrix
314 over modalities to accommodate the different physical nature of signals. This
315 rescaling leads to two crucial aspects: (1) projected data on MEG and EEG spatial
316 modes become homogeneous and (2) sensor-level hyperparameters λ_e and λ_m can
317 be quantitatively compared to assess the relative contribution of each modality to
318 account for the variance of the observed data. Such comparison was conducted
319 using paired Student's t-tests in the case of the MMN inversion ([150,200] ms) in
320 condition FRQ and INT (see below).

321

322

323 **1.2. Quantitative evaluation of separate and fused inversions**

324

325 Bayesian Model Comparison (BMC) is a formal way to quantitatively compare
326 models (M_1, M_2, \dots), based on their inferred model evidence ($p(Y|M_1), p(Y|M_2), \dots$) that
327 each quantifies how likely model M_i is to have generated data Y (Penny et al., 2010).
328 In the present case, for each modality: EEG (e), MEG (m), and Fusion (f), we
329 conducted a BMC that involved three models differing only on the group priors
330 entering individual inversions. The three variants of group priors were inferred by the
331 group-level inversion of EEG data (Y_e), MEG data (Y_m), and fused inversion of EEG
332 and MEG data ($Y_f = [\tilde{Y}_e; \tilde{Y}_m]$) (Figure1.B, step1). These specific models entail the
333 spatial information that could be captured by each modality over the group of
334 subjects, and that we expect to vary across modality. In subsequent individual
335 inversions (Figure1.B, step2), each group prior model will constrain the posterior
336 estimate of source solution relatively to the spatial information conveyed by the
337 inverted data. Our aim was to evaluate the ability of each modality to disentangle
338 between the three resulting source distributions (BMC at the group level) and to
339 compare such performances across modalities. Importantly, our approach is based
340 on model separability whose relation to spatial resolution should be clarified. Spatial
341 resolution usually refers to the finest elements that can be detected or characterized
342 in a 2D or 3D image. However, in the context of EEG and MEG source reconstruction
343 where cortical activity has to be inferred from scalp data by solving an ill-posed

344 inverse problem, a related but different and more important notion is the one of
 345 spatial discriminability or pattern separability. This refers to the ability of the data at
 346 hand to discriminate between two sets of cortical source distribution. Given the highly
 347 non-linear nature of the mapping between source locations and data topographies at
 348 the sensor level, distant sources on the cortical manifold may be harder to separate
 349 than closer ones. From now on, we use the terms spatial resolution, spatial
 350 discriminability or model separability interchangeably, to designate the ability of the
 351 given data, be it EEG, MEG or both, to discriminate between two inverse solutions in
 352 the sense of Bayesian model comparison.

353 To run the evaluation, a total of 9 inversions were computed for each subject: three
 354 modalities for data (mod_d , with $d \in \{e, m, f\}$) combined with three modalities for group
 355 priors (mod_p , with $p \in \{e, m, f\}$). For each data modality (mod_d), the three competing
 356 group prior models denoted M_e , M_m and M_f were confronted to the corresponding
 357 data (Y_{mod_d}), and resulting free energies approximating model evidence $p(Y_{mod_d}|M_e)$,
 358 $p(Y_{mod_d}|M_m)$ and $p(Y_{mod_d}|M_f)$ were thereafter compared across subjects with BMC
 359 using a random effect (RFX) model. This method provides the posterior exceedance
 360 probability of each model, which is the posterior belief that it is more likely than any
 361 others within the considered model space (Stephan et al., 2009). To further refine
 362 how group prior models manifest in inversion performance, we compare model
 363 accuracy (F_a) and model complexity (F_c) across models (for each quantity, 6 one-
 364 tailed paired Student's t-tests: models M_m vs. M_f in MEG and Fusion inversions, and
 365 models M_e vs. M_m in EEG inversion, in both FRQ and INT conditions). Finally, to
 366 account for inter-individual variability, we also computed the following free energy
 367 differences for each subject and for each modality mod_d , approximating the log-
 368 Bayes Factor:

369

$$\mathcal{F}_{mod_d, mod_p=d} - \mathcal{F}_{mod_d, mod_p \neq d} \approx \log \left(\frac{p(Y_{mod_d} | M_{mod_p=d})}{p(Y_{mod_d} | M_{mod_p \neq d})} \right) \quad (5)$$

370

371

372 Following the usual principles of Kass and Raftery (1995), a free energy difference
 373 (in absolute terms) lower than or equal to 3 indicates that models have comparable
 374 evidence: related group priors are of equal plausibility (inseparable models). Under

375 the assumption of non-identical group priors across modalities (EEG, MEG and
376 fusion do not capture the same information), we would thus conclude that modality
377 mod_d is not informed enough to discriminate between these different models. On the
378 contrary, an absolute difference greater than 3 would support a large resolution of
379 mod_d over model space. We expected *i*) EEG to have a poor capacity to separate
380 group prior models, due to volume conduction which is acknowledged to degrade the
381 spatial resolution of EEG (Vallaghé and Clerc, 2009) and *ii*) Fusion to have the
382 largest model separability, being informed by the complementary EEG and MEG
383 (Lopes da Silva, 2013). An original aspect of the proposed approach is that it allows
384 a quantitative comparison of the EEG, MEG and Fusion source reconstructions
385 applied to real data in a thorough way, by providing a detailed description of the
386 inversion performance in each modality and by examining the individual variability in
387 this performance. We carried out this empirical evaluation for the frequency and
388 intensity MMN and early deviance response as described below.

389

390 **1.3. Empirical data for source reconstruction and multimodal evaluation**

391

392 Data originate from a passive auditory oddball study with simultaneous EEG-MEG
393 recordings where the EEG analysis revealed two deviance responses: an early effect
394 occurring within 70 ms after stimulus onset and a late effect (MMN) peaking at 170
395 ms post-stimulus (Lecaignard et al., 2015). We refer the reader to this study for a
396 more detailed description of material and methods.

397

398 1.3.1. *Participants.*

399 27 adults (14 female, mean age 25 ± 4 years, ranging from 18 to 35) participated in
400 this experiment. All participants were free from neurological or psychiatric disorder,
401 and reported normal hearing. All participants gave written informed consent and were
402 paid for their participation. Ethical approval was obtained from the appropriate
403 regional ethics committee on Human Research (CPP Sud-Est IV - 2010-A00301-38).
404 Seven participants were excluded because they paid attention to sounds or their data
405 was of low quality, leading the current analysis based on a total of 20 participants.

406

407 1.3.2. *Experimental design.*

408 Oddball sequences embedding either frequency or intensity deviants (conditions UF
409 and UI in Lecaigard et al., 2015, here renamed as FRQ and INT, respectively) were
410 considered in the present analysis. Both conditions involved the same deviant
411 probability ($p = 0.17$). Two different frequencies ($f_1=500$ Hz and $f_2=550$ Hz) and two
412 different intensities ($i_1=50$ dB SL (sensation level) and $i_2=60$ dB SL) were combined
413 to define the four different stimuli that were used across conditions. Each condition
414 (FRQ, INT) was delivered twice to enable reversing the role of the two sounds
415 (standard and deviant). Further details about stimuli, sequences can be found in
416 Lecaigard et al. (2015). Participants were instructed to ignore the sounds and watch
417 a silent movie of their choice with subtitles.

418

419 1.3.3. *Data acquisition.*

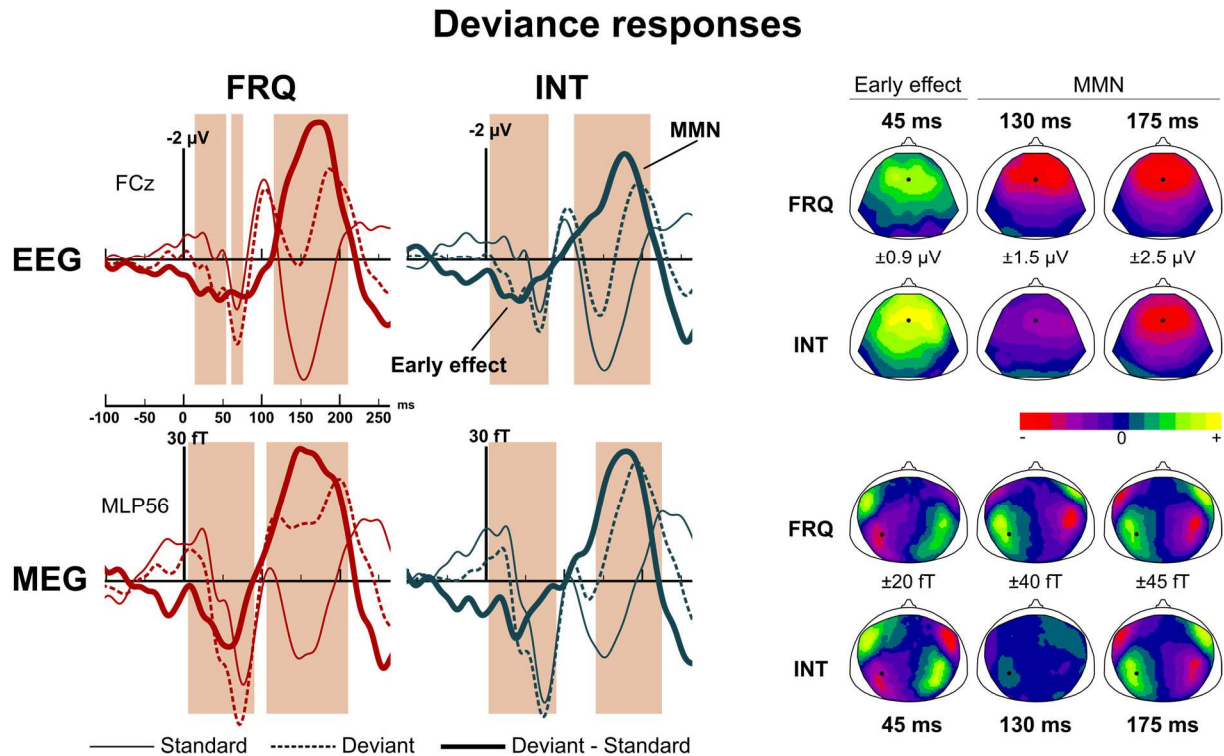
420 Simultaneous MEG and EEG recordings were carried out in a magnetically shielded
421 room with a whole-head 275-channel gradiometer (CTF-275 by VSM Medtech Inc.)
422 and the CTF-supplied EEG recording system (63 electrodes), respectively. We
423 provide here the aspects of particular relevance for the coregistration of multimodal
424 data. Details regarding the simultaneous MEG and EEG recordings and the
425 experimental setup can be found in (Lecaigard et al., 2015). EEG electrode
426 positions relative to the fiducials were localized using a digitization stylus (Fastrak,
427 Polhemus, Colchester, VT, USA) prior to the recordings. Head position relative to the
428 MEG sensors was acquired continuously (sampling rate of 150 Hz) using head
429 localization coils. Special care was taken to minimize head position drifts inside the
430 MEG helmet between sessions. T1-weighted magnetic resonance imaging images
431 (MRIs) of the head were obtained for each subject (Magnetom Sonata 1.5 T,
432 Siemens, Erlangen, Germany). High MRI contrast markers were placed at fiducial
433 locations to facilitate their pointing on MRIs and thereby minimize coregistration
434 errors.

435

436 1.3.4. *Auditory event-related field/potential (ERF/ERP).*

437 MEG evoked responses (2-45 Hz) were computed in exactly the same way as EEG
438 ERPs (Lecaigard et al., 2015), with MEG-specific preprocessings, namely the
439 rejection of data segments corresponding to head movements larger than 15 mm
440 relative to the average position (over the 4 sessions) and to SQUID jumps.

441 Importantly, we only used time epochs that survived the procedures applied for
 442 artifact rejection for both modalities. EEG evoked responses were re-referenced to
 443 the average of the signal at mastoid electrodes in the current study for compatibility
 444 with the forward model. Grand-average responses at gradiometer MLP56 and
 445 electrode FCz in condition FRQ and INT are shown in Figure 2. Permutation tests
 446 (Lecaiguard et al., 2015) revealed an early deviance and an MMN in both modalities
 447 (EEG, MEG) and both conditions.



449 **Figure 2. Mismatch ERPs/ERFs.** Left panel: auditory evoked responses at electrode
 450 FCz (upper row) and gradiometer MLP56 (lower row) for the frequency (left) and
 451 intensity (right) conditions. Shaded areas correspond to the time intervals of
 452 significant mismatch emergence over all sensors (modality-condition): (EEG-FRQ):
 453 [15 55] ms, [65 80] ms, [115 210] ms; (EEG-INT): [5 80] ms, [113 210] ms; (MEG-
 454 FRQ): [5 90] ms, [105 210] ms; (MEG-INT): [3 90] ms, [140 225] ms. Right panel:
 455 scalp topographies at relevant latencies for the early deviance, the rising edge and
 456 the peak of the MMN. Color-scale range is indicated for each map.

457
 458 1.3.5. Data for source reconstruction.

459 We used SPM8 software (Wellcome Department of Imaging Neuroscience,
 460 <http://www.fil.ion.ucl.ac.uk/spm>). Standard and deviant ERFs and ERPs (with
 461 averaged mastoid reference) were down-sampled (200Hz) for data reduction. Source
 462 reconstructions were estimated for difference responses (deviant-standard) in each

463 condition separately (FRQ, INT) and for each modality (EEG, MEG, Fusion). As
464 sensor-level traces showed a tendency for the intensity MMN to start later than the
465 frequency one, we distinguished the rising edge from the peak of this component to
466 increase the spatial sensitivity of reconstructions. Three time windows were thus
467 considered: from 15 to 75 ms (early deviance effect), from 110 to 150 ms (MMN
468 rising edge), and from 150 to 200 ms (MMN peak). Importantly our comparative
469 evaluation of separate (EEG, MEG) and fused (EEG-MEG) inversions was applied to
470 the time interval [150,200] ms in both conditions (FRQ, INT). Regarding data
471 normalization, 7 and 21 spatial modes (explaining 99.0% and 99.9% of the group-
472 informed gain matrix variance) were retained for EEG and MEG, respectively. Data
473 reduction using temporal modes was achieved for all inversions. The number of
474 temporal modes allowing for 100.0% of the variance of the spatially projected data to
475 be explained was equal to 6, 4 and 5 for [15, 75] ms, [110, 150] ms and [150,200] ms
476 time intervals, respectively (for both modalities).

477

478 1.3.6. *Statistical analysis on source distributions.*

479 We conducted our statistical analyses at the group-level using the recent surface-
480 based approach proposed in SPM12. Posterior estimates of source activity and
481 associated variance at each node of the cortical mesh (the source domain) resulted
482 from posteriors of \tilde{J} and C_s . The energy of posterior mean was considered for
483 statistical analysis. One-sample t-tests were performed at each node, thresholded at
484 $p < 0.05$ with Family Wise Error (FWE) whole-brain correction. In addition, we
485 imposed the size of subsequent significant clusters to be greater than 20 nodes.
486 Distance between two local maxima within a cluster was constrained to be larger
487 than 5 nodes.

488

489

490

491 **2. Results**

492

493 We first present the comparative evaluation for EEG, MEG and fused inversions that
494 we conducted with FRQ and INT difference responses, at the MMN peak ([150, 200]
495 ms). Second, as multimodal comparison was in favor of fused EEG-MEG inversion,
496 we report the corresponding sources obtained for the time intervals [15, 75] ms, [110,

497 150] ms and [150,200] ms in the difference responses, in both conditions FRQ and
498 INT, thus applying the current multimodal framework for source reconstruction to the
499 localization of the sources of auditory mismatch responses.

500

501 **2.1. Multimodal evaluation**

502

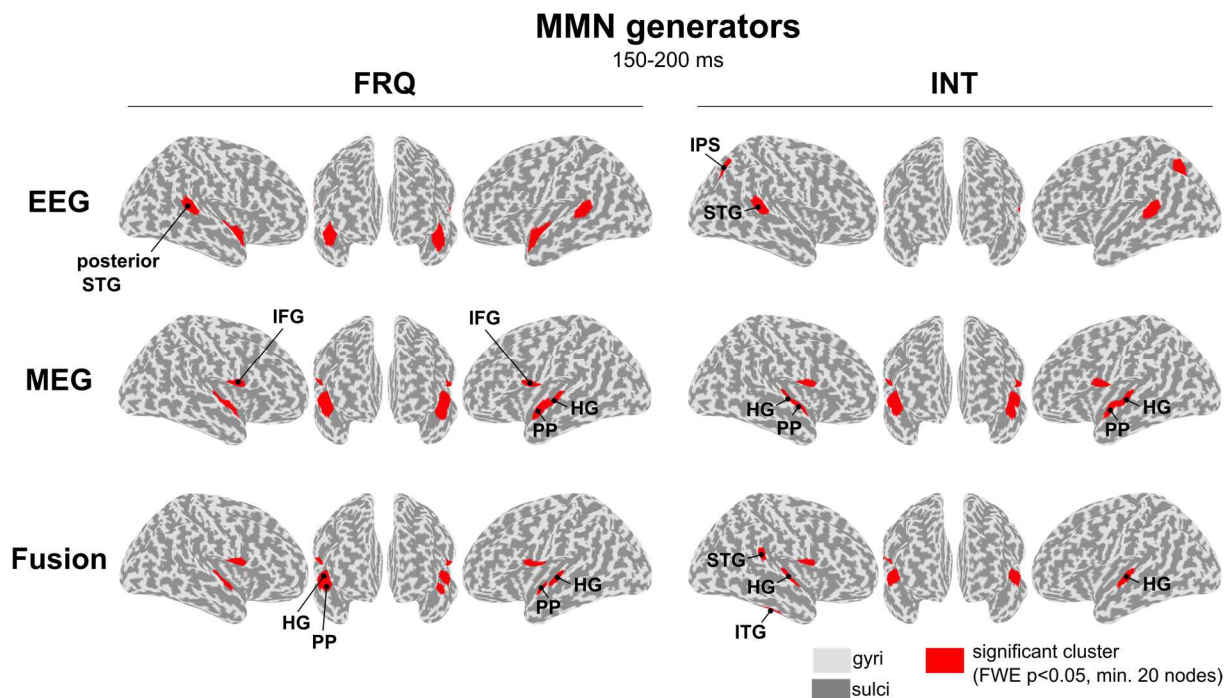
503 Before presenting the results of our evaluation, we begin by controlling that source
504 reconstruction of the MMN peak generators could be computed reliably (in terms of
505 goodness of fit) for each modality and for each subject. This step also enables to
506 point the similarities and differences in group-level results across modalities. We then
507 provide a description of the different group priors obtained in each modality.
508 Evaluation starts by the description of multimodal inversion performance to
509 discriminate between group prior models, followed by a description of findings
510 obtained in the two unimodal cases. These latter assess the respective sensitivity of
511 each modality (EEG,MEG) which helps at better characterizing the outperformance
512 of multimodal integration.

513

514 *2.1.1. Unimodal and fused MMN source distributions (qualitative* 515 *comparison).*

516 The percentage of explained variance in condition FRQ was equal on average to
517 95.1% (± 2.1), 94.2% (± 2.3) and 93.6% (± 2.6) for EEG, MEG and fused inversions
518 respectively. In condition INT, it was equal on average to 94.7% (± 2.5), 93.8% (\pm
519 2.3) and 93.1% (± 2.7) for EEG, MEG and fused inversions respectively. Regarding
520 the contribution of each modality (EEG, MEG) in the case of fused inversion, paired
521 Student's t-tests were used to compare the estimated values of hyperparameters λ_e
522 and λ_m . In both condition FRQ and INT, inversions across subjects led to no
523 significant difference between modalities (FRQ: group-average λ_e/λ_m : 0.018/0.041,
524 $t(19)=1.30$, $p=0.21$; INT: group-average λ_e/λ_m : 0.022/0.051, $t(19)=1.98$, $p=0.06$).

525



527

528

529 **Figure 3. Mean source reconstructions of the MMN obtained in unimodal and**
 530 **multimodal inversions.** Left/Right panel: frequency/intensity MMN ([150, 200] ms,
 531 condition FRQ/INT). Red clusters indicate the significant source activity over the
 532 group ($N=20$) projected on the inflated cortical surface (HG=Heschl's gyrus; STG=
 533 superior temporal gyrus; P=planum polare; IFG=inferior frontal gyrus; IPS= inferior
 parietal sulcus; ITG=inferior temporal gyrus).

534

535 Figure 3 shows the results of the statistical analysis projected on the inflated cortical
 536 surface in each modality (EEG, MEG and EEG-MEG) and each condition (FRQ,
 537 INT). In both conditions, EEG and MEG inversions led to different (but not
 538 inconsistent) reconstructed activity, and more focal clusters were found with fused
 539 inversion. Precisely,

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- In condition FRQ, EEG inversion revealed bilateral activity in the anterior part of the supratemporal plane and in the lower bank of the posterior STG. No frontal area was found significant. MEG inversion indicated a large cluster in the supratemporal plane (number of nodes $k > 120$) expanding from the lateral part of HG through the Planum Polare (PP) in both hemispheres. A bilateral frontal area was located in the posterior IFG. The fused distribution comprised smaller supratemporal clusters (right: a single cluster ($k=92$) including the lateral part of HG and PP; left: separate clusters for HG ($k=55$) and PP ($k=25$)), and bilateral clusters similar to MEG ones in the frontal lobe.

549 • In condition INT, the EEG solution indicated bilateral activity in the posterior
550 STG and the intraparietal sulcus (IPS). There was a similar distribution to
551 condition FRQ with MEG. Fused inversion gave largest contributions in the
552 lateral part of HG in both hemispheres, but also right clusters located in
553 posterior IFG, posterior STG and in the inferior temporal gyrus (ITG).

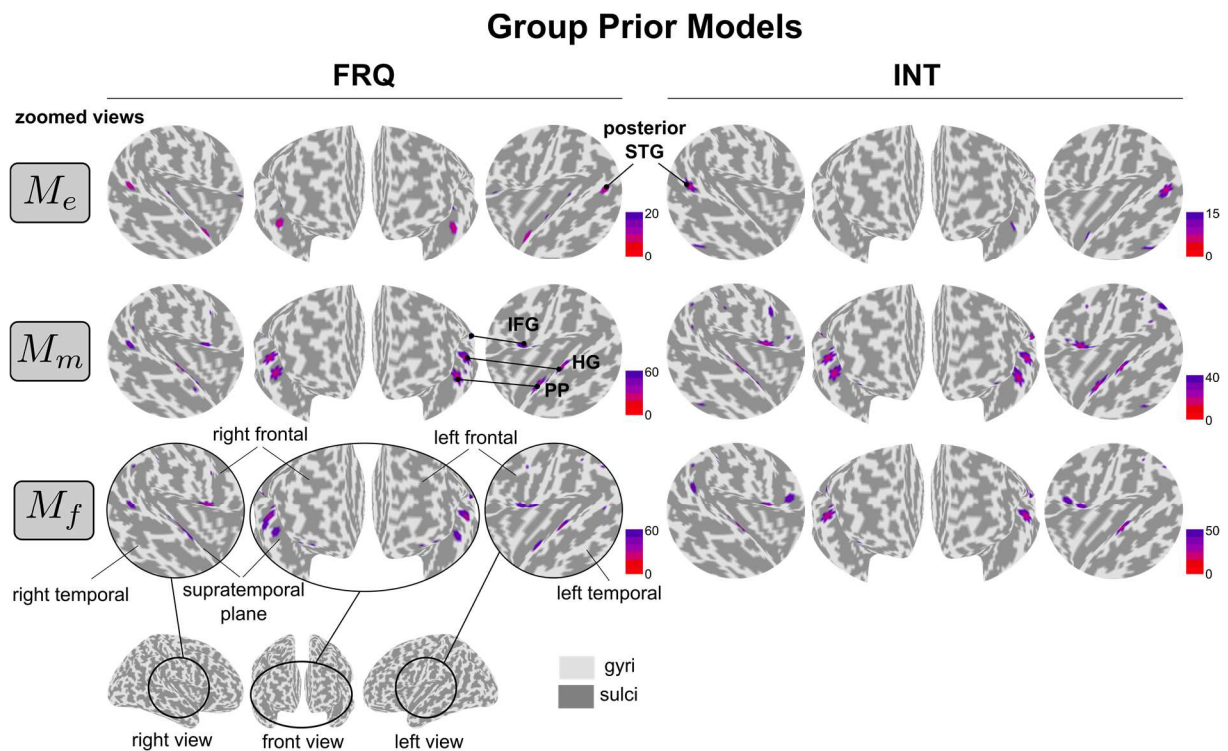
554

555 In sum, this step validates the accuracy of the inversion scheme in each modality,
556 suggests that EEG and MEG contributed equally to the fusion inversion, and finally
557 reveals expected differences in EEG and MEG mean reconstructions that
558 qualitatively motivates the fusion of these modalities to take benefit of their respective
559 sensitivity.

560

561 2.1.2. *Group prior models* (Figure 4).

562 As expected, group priors varied across modalities while showing consistency across
563 the main temporal clusters involved in auditory processing. EEG was found to
564 upweight bilateral priors in posterior STG and the anterior temporal lobe in condition
565 FRQ, and posterior STG, ITG and IPS in condition INT. In both conditions, MEG
566 model upweighted bilaterally the supratemporal plane (lateral HG and PP) and
567 posterior IFG. Fusion priors inferred from both EEG and MEG data involved similar
568 cortical contributions to MEG (except the contribution of PP which was not present in
569 condition INT) suggesting a larger informational value of MEG data. In both
570 conditions and for all modalities, less restrictive priors (smaller cluster size and/or
571 larger variance) were also found that we do not report here for they did not survive
572 any individual inversion.



574

575 **Figure 4. Group prior models for the evaluation scheme.** The three models were
 576 obtained in each modality (EEG, MEG and fusion inversions, separate rows) for the
 577 MMN peak ([150, 200] ms). Left/Right panel: frequency/intensity MMN (condition
 578 FRQ/INT). For each modality and each condition, three zoomed views focusing on
 579 the supratemporal plane (with relation to the global view indicated at the bottom left)
 580 indicate the result of MSP inversion performed at the group level in the first step of
 581 group-level inference. Color scale for the variance of non-null (activated) nodes
 582 (arbitrary units) is mentioned for each model. Similarities of Fusion and MEG models
 583 suggest that MEG data is more informative than EEG about the spatial distribution of
 584 hidden neural generators of auditory responses.

585

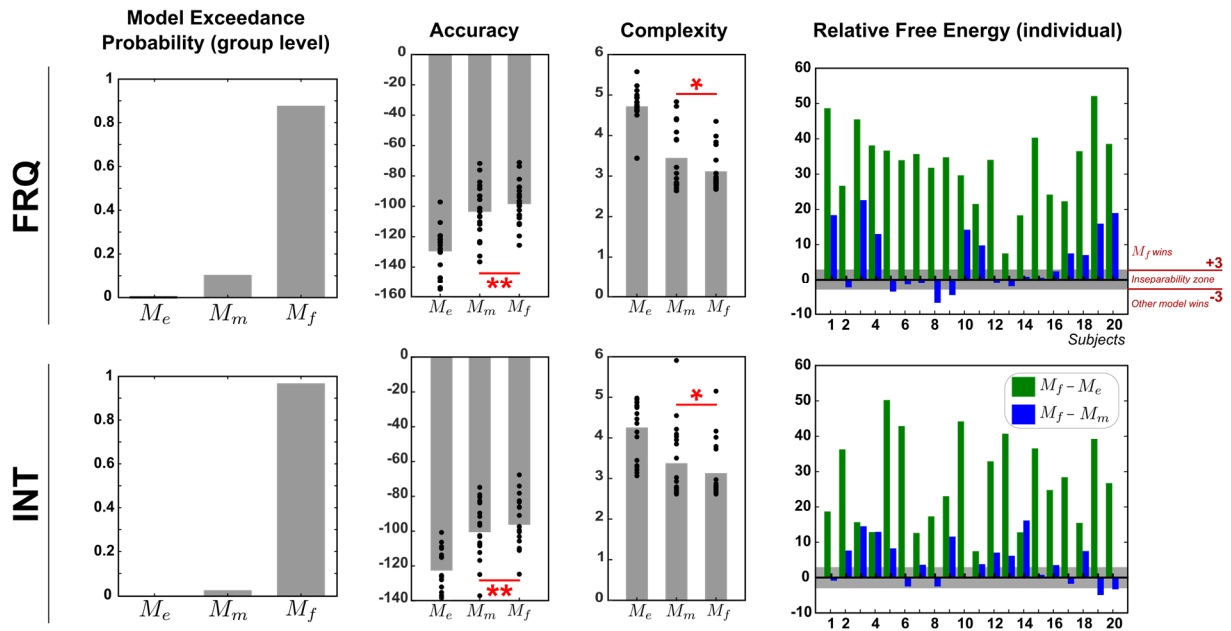
586 2.1.3. Multimodal evaluation (Figure 5).

587 We here describe the results obtained by manipulating the three group prior models
 588 (M_e , M_m and M_f) in the fused inversion. In both conditions, model M_f could be
 589 selected as the winning model at the group level (model exceedance probabilities
 590 given by BMC: $p(M_f|Y_f)=0.88$ and $p(M_f|Y_f)=0.97$ in FRQ and INT, respectively).
 591 This outperformance comes with both an improved model accuracy and a reduced
 592 model complexity relative to MEG model M_m (one-tailed paired Student's t-tests, F_a :
 593 $t > 2.69$, $p < 0.007$ for both conditions; F_c : $t > 2.10$, $p < 0.025$ for both conditions).
 594 Examination of within-subject variability reveals the robustness of model separability

595 across subjects. By setting the evidence threshold to 3, Fusion concludes in favor of
596 model M_f over M_e in all subjects (both conditions), and in favor of model M_f over
597 M_m in the majority of them (9 subjects out of the 12 that did give a conclusive result
598 in FRQ, and 9/14 in INT). This suggests a reduced model separability between M_f
599 and M_m compared to between M_f and M_e , as illustrated in Figure 5, right-most
600 graphs. To further characterize the separation between M_f and M_m , we examined
601 the putative gain or loss of model accuracy and model complexity when replacing
602 original group priors (M_f) by the ones from MEG (M_m). Figure 7.A provides
603 corresponding 2D graphs in the two conditions which clearly reveal the twofold loss
604 (model accuracy and model complexity) obtained at the individual level with MEG
605 priors. Figure 7.A also shows the minority of subjects for whom model M_m was
606 winning over M_f (represented by red dots on the graphs; 3 and 5 subjects in
607 conditions FRQ and INT, respectively). In these singular cases, the same pattern
608 could be observed, namely complexity between models was found nearly equal while
609 the MEG priors systematically yielded a better fit. This suggests that model
610 M_f corresponds to a local minimum for these particular subjects, and illustrates that
611 empirical (group) priors constitute soft constraints on individual solution that can be
612 ruled out when confronted to divergent informative data.

613

Multimodal Inference



614

615 *Figure 5. Model comparison based on fused EEG-MEG data. Group prior model*
 616 *comparison in the fused inversion, for each condition (top row: FRQ, frequency*
 617 *deviance; Bottom row: INT, intensity deviance). On each row, left-most graph:*
 618 *Bayesian model comparison (BMC) of group prior models (M_e , M_m and M_f). Fused*
 619 *priors (M_f) have by far the largest model exceedance probability in both conditions.*
 620 *Middle graphs: model accuracy and model complexity (the two parts of the free-*
 621 *energy, see main text for details): bar and dot plots represent the mean and individual*
 622 *values for each model, respectively. Red stars illustrate the results from the one-*
 623 *tailed paired Student's t-tests (*: $p < 0.05$; **: $p < 0.01$). Right-most graph: the difference*
 624 *in free energy relative to Fusion model for all subjects is plotted as a bar chart*
 625 *(green: EEG model; blue: MEG model). Grey area indicates the zone where models*
 626 *are not separable under an evidence threshold of 3.*

627

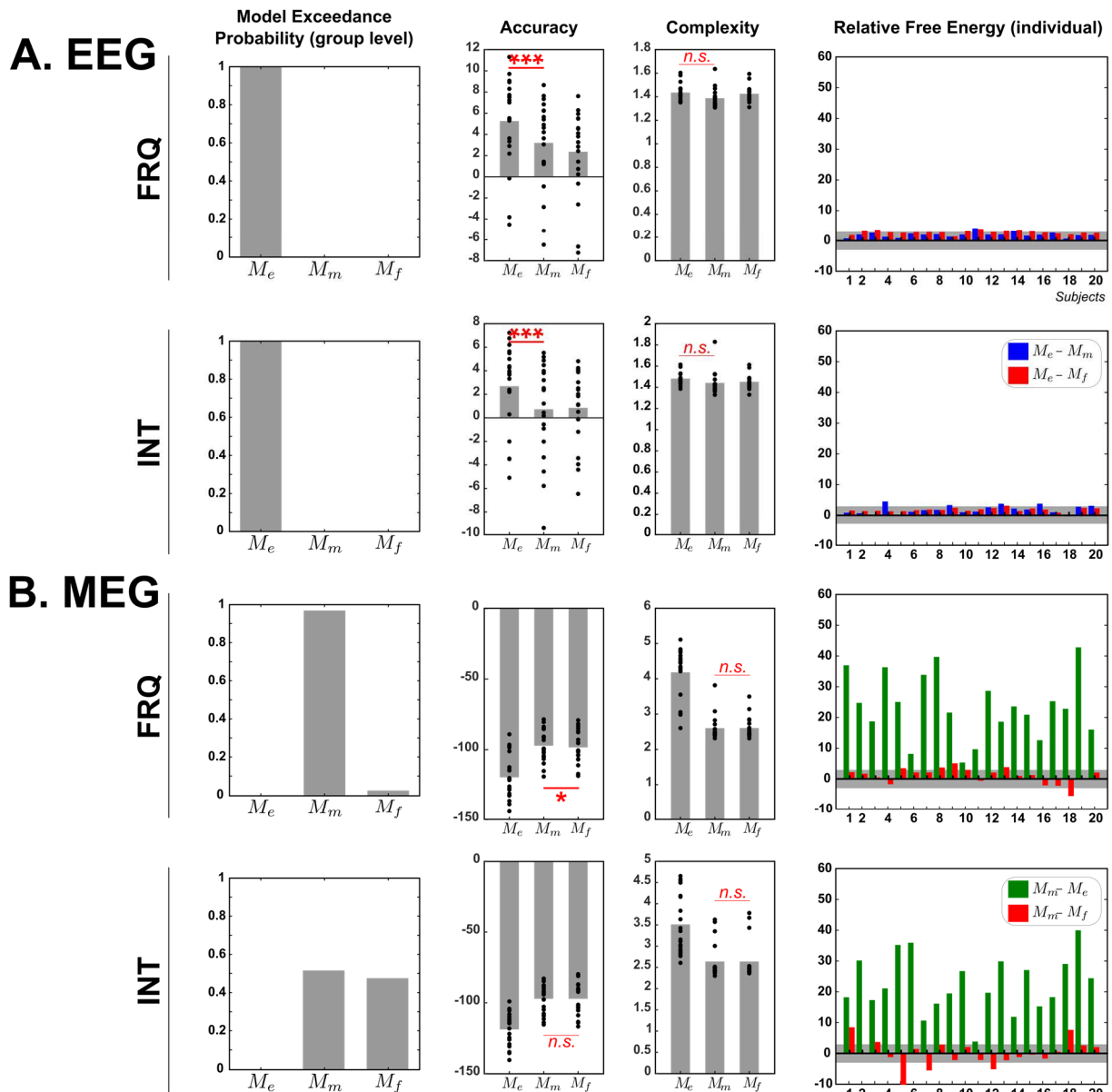
628

629 2.1.4. Unimodal evaluations.

630 Regarding the EEG inversion (Figure 6.A), BMC clearly decided in favor of model M_e
 631 with model exceedance probabilities $p(M_e|Y_e) = 1$ in both conditions. This result
 632 leverages on an increase of model accuracy only (M_e vs. M_m in both conditions, F_a
 633 one-tailed $t > 6.44$, $p < 0.001$; F_c one-tailed $t < -2.35$, $p > 0.98$). However,
 634 examination of individual free energy differences puts the group-level performance
 635 into perspective and rather suggests a poor ability of EEG to separate models.
 636 Precisely, although model M_e could always provide the largest free energy (except in

637 2 subjects with MEG group priors and 1 subject with Fusion priors in condition INT),
 638 low amplitudes of free energy difference prevented from disentangling models. Under
 639 the evidence threshold of 3, models M_e and M_m were not separable in the majority
 640 of subjects in both conditions (18/20, 15/20 in FRQ and INT, respectively), and
 641 similar findings were obtained with M_e and M_f (13/20, 19/20 in FRQ and INT,
 642 respectively).

Unimodal Inference



643 **Figure 6. Model comparison based on EEG and MEG data, separately.** Group
 644 prior model comparison in the EEG (panel A) and the MEG (panel B) inversions.
 645 Results are presented using the same framework as for the multimodal evaluation
 646 (Figure 5). Middle graphs: statistical analysis is indicated (red) whenever it was
 647 conducted (n.s.: non-significant, $p \geq 0.05$; *: $p < 0.05$; **: $p < 0.01$). Right-most graphs:
 648

649 *legend captions in condition INT plots indicate the color code used for the modalities*
650 *concerned in the free energy differences.*

651

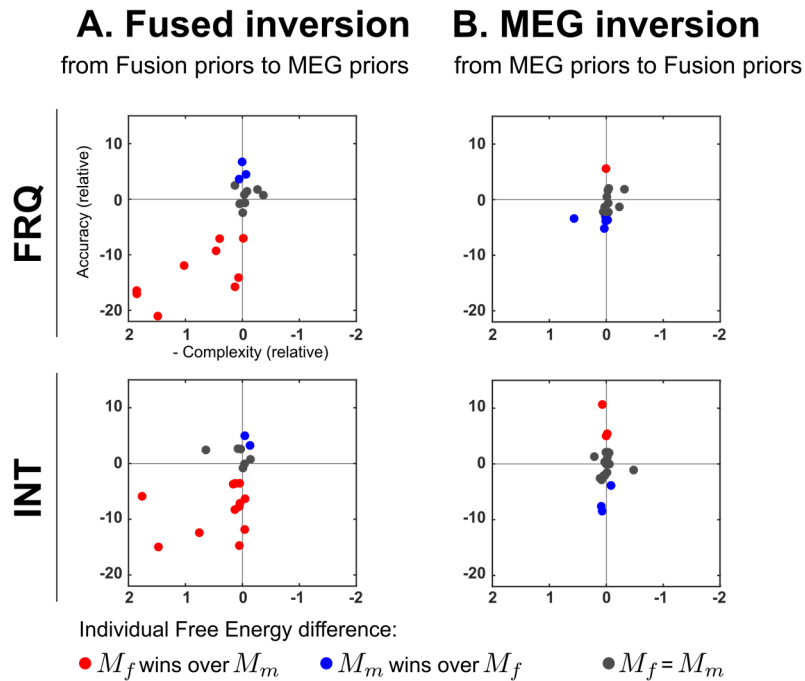
652 Regarding the MEG inversion (Figure 6.B), group-level BMC could separate M_e from
653 M_m in favor of the later model in both conditions. This finding emerges strongly from
654 the large free energy differences observed in all subjects (Figure 6.B right-most
655 graphs). In contrast, separability of MEG and Fusion priors (M_m vs. M_f) appears
656 less clearly and differs across conditions. In condition FRQ, BMC selected MEG
657 priors ($p(M_m|Y_m)=0.97$) which manifest with a larger model accuracy (one-tailed $t =$
658 2.08 , $p = 0.026$) but no significant difference in model complexity (one-tailed $t = 0.07$,
659 $p = 0.473$). Individual inspection shows that MEG inversion led to inconclusiveness in
660 the majority of subjects (14/20) but could select model M_m over M_f in 5 out of the 6
661 remaining subjects. In condition INT, inseparability of models M_m and M_f was found
662 at the group level ($p(M_m|Y_m) = 0.52$ and $p(M_f|Y_m) = 0.48$) and was confirmed by the
663 absence of difference between model accuracy or model complexity (one-tailed $t <$
664 0.03 , $p > 0.487$). Such inseparability was dominant in the group (14/20 subjects) and
665 contrary to condition FRQ, model M_m was not clearly preferred among the 6 other
666 subjects (3/6 preferred M_m , 3/6 preferred M_f). To further address this difference
667 between conditions, that was not present in the fused inversion, we examined the
668 effect of group prior change (from M_m to M_f) in model accuracy and model
669 complexity. Results are shown in Figure 7.B, which discloses a larger within-subject
670 variability in model accuracy in condition INT (number of subjects with
671 improved/reduced accuracy: 10/10 in condition INT; 15/5 in condition FRQ).

672 Finally, an important observation is that in the unimodal inversions, fused priors led
673 predominantly to inseparability when compared to the original group priors (M_e in the
674 EEG inversion, M_m in the MEG inversion) namely 13/20 and 19/20 subjects in the
675 EEG inversion, in condition FRQ and INT, respectively, and 14/20 subjects in the
676 MEG inversion (both conditions).

677

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680

681 **Figure 7. Separability of Fusion and MEG group prior models. A. In the fused**
 682 **inversion.** For each condition, (top/bottom: FRQ/INT) dots represent for all subjects
 683 the change in model complexity as a function of change in model accuracy when
 684 switching from Fusion model (the original priors in the fused inversion scheme) to
 685 MEG model. For a better understanding, the complexity axis has been reversed, so
 686 that the top-left corner of the plot hosts subjects showing a performance
 687 improvement (model change induces larger accuracy, lower complexity) whereas the
 688 bottom-left corner is related to individual degradation. In addition, dots are sorted
 689 according to model separability based on the relative free energy difference (bar
 690 charts in Figures 5 and 6.B) under an evidence threshold of 3. Color code is
 691 indicated in the legend. In both conditions, the majority of subjects show reduced
 692 performance with MEG model, leveraging on both accuracy and complexity terms. B.
 693 **In the MEG inversion.** The plots here indicate the changes when replacing the
 694 original MEG priors by the Fusion model. Here, these 2D representations reveal the
 695 lack of effect on complexity in both conditions, and the larger inhomogeneity of the
 696 group in the INT condition, as the group splits into two parts of equal size along the
 697 accuracy dimension.

698

699 2.1.5. Summary.

700 Our evaluation approach relying on group prior model comparison succeeded at
 701 quantifying the performance of each modality for the reconstruction of empirical data.
 702 We found a large and robust model separability in the multimodal inversion, where
 703 the integration of EEG and MEG data enabled to enhance model accuracy and
 704 reduce model complexity. Such performance could not be achieved with unimodal
 705 inversions. Precisely, EEG exhibited a poor ability to discriminate between the three
 706 models, as evidenced by the majority of individual indeterminations encountered in

707 both conditions. The MEG inversion proved to be similar to the Fusion scheme for
 708 separating and selecting original priors against EEG ones, but revealed limited
 709 performances with Fusion priors, an effect that was further found sensitive to inter-
 710 individual variability. The twofold better performance of MEG over EEG (more
 711 plausible spatial priors with unimodal and multimodal inferences, and larger spatial
 712 discriminability) speaks to the fact that MEG was found here more informative than
 713 EEG. Moreover, and interestingly, its failure to reach the multimodal performance
 714 also ascertains its complementarity with EEG. In the following section, we present
 715 the deviance-related source reconstructions inferred from multimodal data, here
 716 evidenced as the most informative modality.

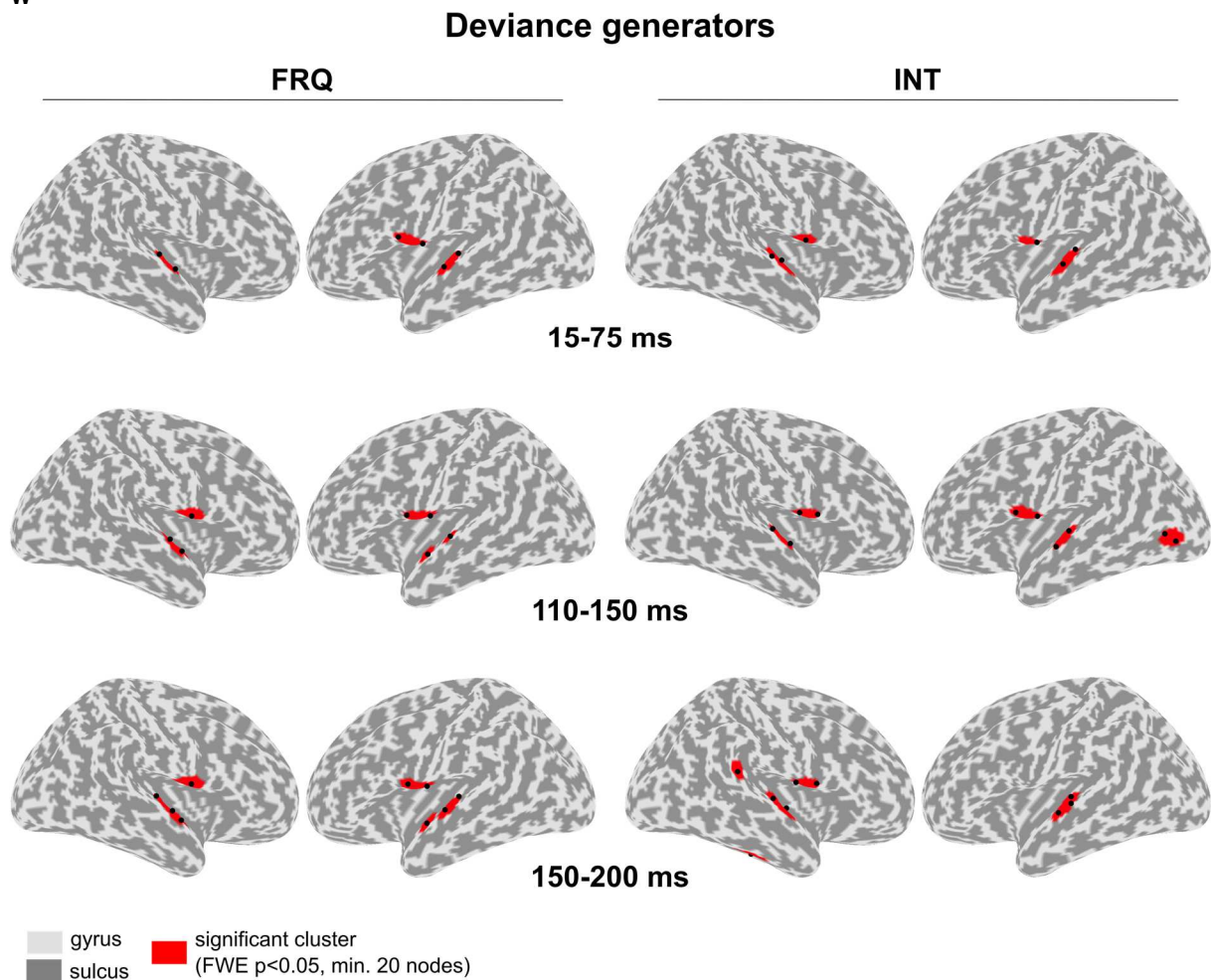
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718 **2.2. Fused EEG-MEG sources for auditory mismatch responses**

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723 **Figure 8. Deviance generators (fused MSP reconstruction).** Significant clusters
 724 (red) are displayed on the inflated cortical surface (right and left views) for each time
 725 interval (rows) and each condition (frequency=left panel, intensity=right panel). Black
 726 dots indicate the local maxima within each cluster (with a minimum distance of 5
 727 adjacent nodes). MNI coordinates are provided in Table 1 (frequency) and Table 2
 728 (intensity).

729
 730 Figure 8 shows the results obtained for each deviance type and each time interval
 731 with fused inversion. Cluster sizes and peak location in MNI space for each local
 732 maxima for significant activated areas are summarized in Table 1 for condition FRQ,
 733 and Table 2 for condition INT.

734

735 2.2.1. Condition FRQ.

736 Reconstructions of deviance generators within time windows [15, 75] ms, [110, 150]
 737 ms and [150,200] ms were performed with the percentage of explained variance
 738 equal on average to 90.7% (± 4.8), 92.3% (± 4.4) and 93.6% (± 2.6), respectively.
 739 Early-deviance effect ([15, 75] ms) was found to involve HG in both hemispheres and
 740 left posterior IFG. Following this, reconstruction of the rising edge of the MMN ([110,
 741 150] ms) indicated supratemporal activity in HG and PP, within a large cluster in the
 742 right hemisphere (comprising two local maxima), and separated in two distinct
 743 clusters in the left hemisphere (with HG cluster being smaller). Significant activity
 744 was also found in bilateral posterior IFG. Finally, as described in previous section,
 745 the peak of the MMN ([150,200] ms) was associated with activity in both
 746 hemispheres peaking in HG, PP and posterior frontal IFG. The total number of
 747 significant nodes within bilateral supratemporal planes was larger for the peak than
 748 for the rising edge of the MMN (178 and 108 respectively), while it remained constant
 749 within IFG (116 and 112 respectively).

750

FRQ	Side	Source	Cluster Size	Peak Location		
		Cluster				
<i>Early deviance, [15 75] ms</i>	L	HG	56	-60	-9	2
				-45	-23	7
	R	HG	57	59	-3	2
				48	-17	6
	L	IFG	50	-53	10	15
			-58	-2	2	

<i>MMN Rising Edge, [110 150] ms</i>	L	HG	19	-54	-12	4
	L	PP	21	-49	-8	-10
	R	HG/PP	68	52	-8	4
				49	-7	-8
<i>MMN Peak, [150 200] ms</i>	L	IFG	57	-56	6	9
				-56	-6	8
	R	IFG	55	57	2	6
	L	HG	55	-60	-9	2
				-45	-23	7
	L	PP	25	-50	-6	-8
	R	HG/PP	92	55	-5	4
				48	-19	6
				49	-7	-8
	L	IFG	55	-56	6	9
			-53	-6	6	
R	IFG	61	57	2	6	

751

752 *Table 1. Results of MSP inversion for frequency deviance with fused inversion.*
753 *Cluster Size: number of cortical mesh nodes. Peak Location: MNI coordinates in mm.*

754 **2.2.2. Condition INT.**

755 The percentage of explained variance was equal on average to 91.4% (± 5.2), 90.5%
756 (± 5.4) and 93.1% (± 2.7) for the reconstructions within time windows [15, 75] ms,
757 [110, 150] ms and [150,200] ms, respectively. Within the early-deviance window ([15,
758 75] ms), activity was mostly found in bilateral HG but was also located in posterior
759 IFG. Reconstructions within [110, 150] ms produced significant clusters in bilateral
760 HG and posterior IFG. In addition, there was a spurious contribution from left middle
761 occipital gyrus (MOG). Finally, sources in HG and posterior IFG were observed in
762 both hemispheres for the MMN peak reconstruction ([150,200] ms). Smaller clusters
763 were found in ITG and posterior STG in the right hemisphere. With the thresholds
764 chosen in the current study, no contribution of PP could be reported at any latency.

765

INT	Source		Cluster Size	Peak Location		
	Side	Cluster				
<i>Early deviance, [15 75] ms</i>	L	HG	70	-58	-10	5
				-43	-25	9
	R	HG	71	49	-11	4
				55	-16	3
	L	IFG	28	-58	-2	2
	R	IFG	37	57	2	6

<i>MMN Rising Edge, [110 150] ms</i>	L	HG	55	-48	-18	5
				-59	-11	-5
	R	HG	56	59	-3	2
				48	-17	6
	L	IFG	57	-55	8	13
				-58	-2	2
	R	IFG	45	51	9	5
				57	0	12
	L	MOG	46	-41	-74	-1
				-40	-74	4
<i>MMN Peak, [150 200] ms</i>	L	HG	76	-45	-20	6
				-61	-9	-2
				-60	-18	2
	R	HG	77	49	-16	3
				50	-9	0
	R	STG	33	62	-37	20
	R	ITG	31	57	-29	-27
	R	IFG	46	51	6	5
				51	-3	14

766

767 *Table 2. Results of MSP inversion for intensity deviance with fused inversion. Cluster*
768 *Size: number of cortical mesh nodes. Peak Location: MNI coordinates in mm.*

769

770

771 2.2.3. *Summary.*

772 The fused reconstructions of deviance responses observed in ERP/ERF revealed a
773 bilateral fronto-temporal network in both conditions (FRQ, INT). Temporal activity
774 was clustered in the supratemporal plane, where fused inversion improved the
775 spatio-temporal description of deviance-related activity. In particular, fused inversion
776 could separate HG and PP clusters spatially, but also temporally as PP contribution
777 varies over time and across conditions. Frontal contributions could be recovered in
778 both conditions as soon as the early deviance window.

779

780

781 3. Discussion

782

783 In the present study, we proposed an original and generic approach to address the
784 long-standing question of the benefit of EEG-MEG data fusion to infer cortical
785 activity. This approach rests on hierarchical empirical Bayesian modelling and
786 Bayesian model comparison to disentangle between alternative spatial models using
787 empirical data. This departs from most former fusion approaches that could only be
788 formally evaluated using simulated data. Furthermore, in contrast with previous
789 Bayesian approach (Henson et al., 2011), we conduct this assessment in the context
790 of group level inference, which enables the formal comparison of spatial priors
791 derived from unimodal and multimodal group data at the individual level. To our
792 knowledge, the method used here is also the first to combine: realistic forward
793 modelling, hierarchical empirical Bayesian inference, group-level and fused EEG-
794 MEG inference, and surface-based statistics. Finally, we applied this framework to
795 the important issue of localizing the sources of the auditory MMN, a component that
796 is very much studied and used as a marker of perceptual processes and their
797 alterations in various neurological and psychiatric conditions (Carbajal and
798 Malmierca, 2018; Friston, 2005; Näätänen et al., 2012).

799 Our results conclude in favor of the superiority of data fusion for source
800 reconstruction in this context. Importantly, model comparisons at the group level and
801 then at the individual level also shed light on the specific characteristics of each
802 modality and on the complementarity of the EEG and MEG. This aspect is rarely
803 examined with real data, in a quantitative manner. Fused inversion applied to early
804 and late deviance responses resulted in a fronto-temporal network consistent with
805 existing findings obtained from EEG or MEG alone, but described here, to our
806 knowledge, with an unprecedented spatio-temporal finesse.

807

808 ***A formal approach to compare unimodal and multimodal inference for source*** 809 ***reconstruction.***

810 Our approach offers an alternative to the one proposed by Henson et al. (2011)
811 which also relied on the Bayesian framework to evaluate the benefit of EEG and
812 MEG data fusion. As noted by the authors, "*Because the model evidence is*
813 *conditional on the data, one cannot evaluate the advantage of fusing MEG and EEG*
814 *simply by comparing the model evidence for the fused model relative to that for a*

815 *model of the MEG or the EEG data alone*". They circumvented this obstacle by
816 comparing three alternative models for the multimodal inference, varying the
817 measurement noise prior of EEG and MEG to simulate unimodal EEG data (MEG
818 data is only noise), MEG data (EEG is only noise) and multimodal data (EEG and
819 MEG are both informative). A formal model comparison concluded that fusion is the
820 most informative approach and that MEG is more informative than EEG.

821 In contrast we adopted a two-step approach that we applied for unimodal and
822 multimodal inference. First, using a fixed effect analysis, we derived the most likely
823 subset of sources at the group level, given each unimodal data or multimodal data.
824 This led to three alternative models which we could then compare formally, at the
825 individual level, based either on fused EEG and MEG data, or EEG and MEG data
826 taken separately. This is interesting because it enables to assess, for each modality
827 independently, how much this modality is able to distinguish between different but
828 plausible sets of source locations. And given that these prior sets of locations reflect
829 the sensitivity of each modality, this enables to compare EEG, MEG and fusion in
830 their ability to reproductively select spatial models derived from the same data type
831 over subjects, or on the contrary, to show poor specificity by expressing no
832 preference.

833 Of course, it should be borne in mind that, as in the work by Henson et al. (2011), our
834 framework for model comparison rests on the Variational Bayes (VB) approximation
835 to the model log-evidence (the free energy) which could potentially impact the
836 outcome of model selection. This issue was precisely addressed in Friston et al.
837 (2007), using synthetic EEG data, in a context very similar to ours (hierarchical linear
838 generative models). Not only BMC was found to recognize the true generative model
839 of the simulated data among alternative candidates, but VB log-evidence
840 approximations for all models were found very close to the ones obtained with
841 MCMC, a sampling method assumed to provide an exact inference (but see also
842 Litvak et al., 2019 in the case of hierarchical non-linear dynamic models). These
843 previous findings demonstrated the face validity of VB for BMC in this context.
844 Furthermore, our comparison between modalities was here further supported by the
845 separate report and assessment of model Accuracy and Complexity. These analyses
846 were in line with the outcome of BMC based on the free energy and afforded a
847 further refined description of the relative specificity of EEG, MEG and data fusion.

848 The present procedure proves to be very rich in lessons, as modalities could be
849 compared in terms of both the spatial priors they provide, and the spatial
850 discriminability they enable. This is nicely illustrated by our findings with EEG and
851 MEG taken alone. Indeed, EEG and MEG estimated different contributions from
852 temporal and frontal sources, hence reflecting their different spatial sensitivity.
853 However the source distribution inferred with EEG was mostly rejected by the MEG
854 data as a poor model, but not the other way round.

855 Overall, this approach, here applied to auditory data, led to several important
856 findings: notably the weak spatial discrimination power of the EEG; the higher
857 sensitivity of MEG to inter-subject variability, which goes along with a higher spatial
858 discrimination power; the robustness of multimodal inference which compensates for
859 these limitations of unimodal inference (see below for further discussion).

860
861

862 ***About the difference and complementarity of EEG and MEG recordings.***

863 The empirical evaluation we performed in two separate conditions, for reproducibility,
864 shows that the inference based on multimodal data was able to finely discriminate
865 between alternative plausible spatial priors, and to select the most informed one (the
866 group prior derived from combined EEG and MEG data), in most subjects. Precisely,
867 the higher free energy afforded by the multimodal priors was driven by both a higher
868 accuracy and a reduced complexity.

869 This contrasts with what we observed with the unimodal based inferences, where
870 model complexity was not improved by considering the group prior from the same
871 modality. This is important because, taken together, these results promote
872 multimodal integration not only because it provides a higher goodness of fit, as
873 traditionally observed with simulation-based studies, but also because it offers a
874 generalizable solution over subjects. In other words, multimodal inference yielded a
875 highly plausible solution common to all subjects, which also provides optimal priors at
876 the individual level to accommodate the between-subject variability.

877 As a validity check, we controlled that the two modalities were indeed afforded similar
878 weighting by the empirical multimodal Bayes inference. In agreement with Henson et
879 al. (2011) findings, we found no significant difference between precision noise

880 parameters at the sensor level¹. This confirms that the superiority of multimodal
881 inference is indeed due to a combination of EEG and MEG recordings.

882 Of course, this is to be concluded in the context of auditory mismatch responses.
883 However, it is likely to be generalizable to any brain regions whose activity can be at
884 least partly captured by both EEG and MEG sensors.

885

886 Our evaluations of unimodal inferences helped further characterizing the
887 complementarity between EEG and MEG which are assumed to capture different
888 aspects of the same underlying biophysical phenomena (Lopes da Silva, 2013). An
889 illustration was given here where, at the scalp level, a difference in topographies
890 between the frequency and intensity MMN could only be clearly observed with MEG.
891 It is well known that EEG and MEG are not sensitive to the same source locations
892 and orientations, as well as to the same biophysical properties of the head tissues
893 (Lecaigard and Mattout, 2015). This certainly explains the differences in
894 performance and source distributions here obtained with EEG and MEG based
895 inference, respectively (Figure 3). Remarkably, our procedure allows to reveal and
896 operationalize those differences.

897 Precisely, EEG proved able to extract relevant group-level priors that could best
898 constrain individual inversions (model M_e obtained a very high exceedance
899 probability at the group level when using EEG data alone). This clearly ascertains
900 that EEG can be used reliably for source reconstruction studies, at least in the
901 auditory domain. However, individual inspection reveals a rather weak ability to
902 distinguish between spatial models across an homogeneous group of subjects
903 (superiority of model M_e is a non-significant effect but present in all subjects). The
904 MEG and Fusion models provided different group-informed cortical solutions (as can
905 be seen notably in the supratemporal regions, Figure 4) but they turned out to be
906 plausible alternative candidates in the eyes of EEG. This clearly resonates with the
907 expected poorer spatial resolution with EEG (Puce and Hämäläinen, 2017).

908

909 This work also provides new perspectives on the information conveyed by MEG
910 signals. The MEG model qualitatively exhibited more similarities with the Fusion

¹ Note that this finding was obtained under the commonly used assumption of independent and identically-distributed sensor noise. This assumption yields limited effect on data scaling performed during the inversion as suggested in Henson et al. (2009) with MEG.

911 model than with the EEG one (Figure 4). This suggests that fusion priors were
912 primarily informed by MEG data, which, in a Bayesian setting, should be related to
913 greater reliability. Furthermore, in multimodal inference, the MEG model was not
914 selected but showed a smaller separability with the winning Fusion model than the
915 EEG model (this is clearly visible on the individual bar charts in Figure 5, which
916 enables to compare the evidence in favor of each model). Hence MEG appears as
917 significantly more informative than EEG, in the present case of auditory data. This is
918 again in full agreement with the expected higher spatial resolution with MEG than
919 EEG (Babiloni et al., 2009) , and in particular within the temporal lobe (Poepffel and
920 Hickok, 2015).

921 However, MEG data alone in condition INT, failed to separate the MEG and Fusion
922 models. This results may be attributable to the group heterogeneity, which was not
923 observed in the other two modalities. This speaks again for a higher spatial sensitivity
924 of MEG recordings, whose consequence here would be that precise group-informed
925 solutions become likely to be less accepted at the individual level in the few subjects
926 who most deviate from the group (conversely, the EEG suffering from greater spatial
927 blurring would be less sensitive to between-subject variability). Most importantly, the
928 integration of EEG with MEG data (Fusion model, and multimodal inversion) enables
929 to resolve this issue.

930

931 ***About the generators of Mismatch responses.***

932 The comparative analysis performed at the peak of the MMN strongly encouraged us
933 to merge EEG and MEG data to finely characterize the sources of other mismatch
934 responses, as never done before. The main finding of this subsequent analysis is the
935 identification of a bilateral fronto-temporal network at play during early and late
936 deviance responses, for both conditions (FRQ, INT). The MMN findings (including the
937 rising edge and the peak of the MMN) is totally consistent with the existing literature
938 supporting fronto-temporal generators (Andreou et al., 2015; Auksztulewicz and
939 Friston, 2015; Fulham et al., 2014; Lappe et al., 2013b; Marco-Pallarés et al., 2005;
940 Recasens et al., 2014b; 2015; Rinne et al., 2000; Schairer et al., 2001). Perhaps the
941 most striking point in comparison with these EEG or MEG studies is that expected
942 contributions (frontal and temporal, bilateral) could be all identified at once and with a
943 far larger spatial specificity (in the supra-temporal plane in particular) than usually
944 observed. The present findings rather resemble those obtained with fMRI, as

945 reported by Schönwiesner and collaborators (2007). From a qualitative point of view,
946 fused inversion could thus reach the spatial resolution of fMRI (at least in the
947 temporal lobe), which made possible to reveal distinct spatial patterns across specific
948 time intervals in the first 200 ms of auditory processing (which is obviously not
949 feasible with BOLD signals). In particular, we could observe a posterior to anterior
950 progression in the supratemporal plane (from HG to PP), between the rising edge
951 and the MMN peak for the frequency condition, in line with several studies that
952 explored the N1 and MMN generators (Recasens et al., 2014a; Scherg et al., 1989).
953 Note also, that the comparison of the frequency and intensity conditions shows subtle
954 spatio-temporal patterns: similar activations at early latency are followed by
955 differences within the supratemporal plane and frontal regions during the MMN. This
956 supports different sensory processes at the MMN latency, as proposed by early ECD
957 studies conducted with EEG (Giard et al., 1995) and MEG (Levänen et al., 1996).
958 Regarding early deviance generators, temporal activity was clearly circumscribed
959 within bilateral Heschl's gyrus for both deviance features. This is totally consistent
960 with MLR findings from intracranial recording studies (Liégeois-Chauvel et al., 1994;
961 Pantev et al., 1995; Yvert et al., 2002). Recent MEG studies also reported temporal
962 contributions including from HG, in the right hemisphere (Recasens et al., 2014a)
963 and bilaterally (Recasens et al., 2014b). Crucially, a major difference with these
964 studies pertains to frontal sources that we were able to recover. Under the
965 assumption of a hierarchical anatomo-functional organization for deviance
966 processing, which would cover subcortical areas up to associative cortical regions
967 (Escera and Malmierca, 2014), such early frontal contributions are quite expected.

968

969

970 Some slightly surprising findings reported here should however be discussed, like the
971 failure to identify any frontal source with EEG, at the MMN latency. A careful
972 inspection of the MMN literature reveals that it is indeed not straightforward to detect
973 IFG activation from EEG responses, unless one considers specific priors with
974 discrete ECD models (Jemel et al., 2002; MacLean et al., 2015; Rissling et al., 2014).
975 However, two studies using distributed source models did report a contribution from
976 IFG (Fulham et al., 2014; in a language study: Hanna, 2014). In our case, it is likely
977 that inferior frontal activations were less plausible (possibly weaker) than supra-
978 temporal ones, and as such they have been discarded by MSP, which incorporates a

979 sparsity constraint. It should also be noted that few MEG studies also succeeded in
980 localizing these regions (Lappe et al., 2013b; Recasens et al., 2015).

981 Another unexpected result pertains to the contribution of the left middle occipital
982 gyrus and the right inferior temporal gyrus for intensity deviance with fused inversion.
983 It is worth recalling that the intensity MMN was not significant at the scalp-level over
984 the time interval between 100 and 150 ms. We therefore assume that these sources
985 are false positive. Finally, frontal contributions were located in the very posterior part
986 of the IFG, just above supratemporal regions. However, the fact that we observed
987 activations in IFG but not in PP (rising edge of the MMN, INT) and in HG but not in
988 IFG (peak of the MMN, INT) allows to reject the hypothesis of two mis-localized and
989 correlated clusters of opposite sign.

990

991

992 **Conclusion**

993

994 This paper develops an evaluation procedure to assess the benefit of fusing EEG
995 and MEG data for distributed source localization. Critically, it offers a generic
996 approach that is applicable to empirical data. It thus paves the way to go beyond
997 simulations to evaluate the gain in performance afforded by multimodal integration.
998 Importantly, this assessment is data dependent. This means that one could assess
999 the relative importance of combining EEG and MEG recordings, for a given cortical
1000 network (e.g. associated with a particular type of perception or cognitive tasks) and a
1001 given population of subjects (e.g. with more or less heterogeneity). In the present
1002 example of studying auditory mismatch responses, multimodal integration proved to
1003 outperform unimodal inference, as expected, and can now be highly advised for
1004 future studies in the field. We could indeed identify a bilateral fronto-temporal network
1005 for both frequency and intensity deviance responses which is in accordance with the
1006 existing literature. Promisingly, the spatial resolution reached with fused inversion
1007 allowed a detailed spatio-temporal description within the supratemporal plane. These
1008 findings should however be balanced against the experimental cost of simultaneous
1009 EEG-MEG acquisitions that remain somewhat less straightforward than unimodal
1010 ones. The detailed auditory network reconstructed here represents a crucial step for
1011 future studies that will aim at addressing the fine neurophysiological and
1012 computational mechanisms underlying auditory processing.

1013

1014

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1029

1030 ***Appendix. The Free Energy approximation***

1031 Variational Bayes (VB) enables a simultaneous twofold inference, on models and
1032 model parameters, respectively (Beal, 2003; Starke and Ostwald, 2017). The former
1033 rests on an approximation to the model log-evidence (the variational free-energy),
1034 and the latter is provided by the (Laplace approximate) variational posterior
1035 distribution. Denoted by F and given the model M with parameters θ , the variational
1036 free-energy is such that:

1037

$$\log p(Y|M) = F(M) + \text{KL}[q(\theta), p(\theta|Y, M)] \quad (\text{A.1})$$

1038

1039 The left hand term corresponds to the model Log-evidence and $q(\theta)$ indicates the
1040 variational posterior distribution which is updated to maximize free energy and
1041 approximate the true posterior $p(\theta|Y, M)$. KL is the Kullback Leibler divergence and
1042 measures the discrepancy between any two probability densities. It writes:

1043

$$KL[q(\theta), p(\theta|Y, M)] = \int q(\theta) \log \frac{q(\theta)}{p(\theta|Y, M)} \quad (A.2)$$

1044

1045 Importantly, KL equals zero when the two densities are equal, and is greater than
 1046 zero otherwise. This means that the free energy is a lower bound to the log-evidence.
 1047 Variational inference consists in updating $q(\theta)$ to maximize free energy so that, at
 1048 convergence

$$\begin{aligned} q(\theta) &\approx p(\theta|Y, M) \\ F(M) &\approx \log p(Y|M) \end{aligned} \quad (A.3)$$

1049

1050 As an approximate to model evidence, F can be used for model comparison and
 1051 selection (Penny et al., 2007). Interestingly, it can be rewritten as follows:

$$F(M) = \int q(\theta) \log p(Y|\theta, M) d\theta - KL[q(\theta), p(\theta)] \quad (A.4)$$

1052 The first term on the right hand side is an accuracy term, the marginal log likelihood.
 1053 The second term is a complexity (penalty) term, the KL divergence between the
 1054 variational and the prior. An important aspect disclosed by this formulation is that
 1055 letting $q(\theta)$ departing from prior $p(\theta)$, which happens if data Y is not fully compatible
 1056 with prior $p(\theta)$, increases model complexity and should thereby be compensated by a
 1057 better fit of data Y (a larger accuracy) in order to maximize $F(M)$.

1058

1059 Variational free-energy affords an approximation to the log Bayes Factor introduced
 1060 by Kass and Raftery (1995) to compare two models based on their relative log-
 1061 evidence after confrontation to the same data Y . Given equation A.3, the log Bayes
 1062 Factor for model M_i with respect to model M_j writes as follows:

$$\log BF_{i,j} = \log \frac{p(Y|M_i)}{p(Y|M_j)} \approx F(M_i) - F(M_j) \quad (A.5)$$

1063

1064 This approximation enters the general Bayesian Model Comparison (BMC) to select
 1065 the most plausible model among several candidates, which is central to the proposed
 1066 evaluation scheme where model space comprises three group prior models
 1067 $(\{M_{EEG}, M_{MEG}, M_{Fusion}\})$.

1068

1069 In the context of models for neuroimaging data, the variational free-energy has
1070 shown to surpass other common approximate metrics for model comparison, namely
1071 the Akaike's Information Criterion (AIC) and the Bayesian information criterion (BIC)
1072 (Penny, 2012). Furthermore, it has been validated against exact but computationally
1073 prohibitive Monte-Carlo estimates of the log-evidence (Friston et al., 2007). It can be
1074 used to compute Bayes factors, model posteriors and model exceedance
1075 probabilities.

1076

1077 **CRedit Author Statement**

1078 Conceptualization, AC, FL and JM; Methodology, FL and JM; Software, FL and JM;
1079 Investigation, AC and FL; Writing, AC, FL and JM; Funding Acquisition, OB, AC and
1080 JM; Supervision, OB, AC and JM.

1081

1082 **Declaration of Interest**

1083 The authors declare that they have no conflict of interests.

1084 **Ethic Statement**

1085 The authors state that written informed consent was obtained from participants.
1086 Ethical approval was obtained from the appropriate regional ethics committee on
1087 Human Research (CPP Sud-Est IV - 2010-A00301-38).

1088

1089 **Data and Code Availability Statement**

1090 The data and code that support the findings of this study are available from the
1091 corresponding author upon request.

1092

1093

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