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1 **The auditory evoked-gamma response and its relation with the N1m.**

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18

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Abstract

21 This study explored the patterns of oscillatory activity that underpin the N1m auditory evoked
22 response. Evoked gamma activity is a small and relatively rarely-reported component of the auditory
23 evoked response, and the objective of this work was to determine how this component relates to the
24 larger and more prolonged changes in lower frequency bands. An event-related beamformer
25 analysis of MEG data from monaural click stimulation was used to reconstruct volumetric images and
26 virtual electrode time series. Group analysis of localisations showed that activity in the gamma band
27 originated from a source that was more medial than those for activity in the theta-to-beta band, and
28 virtual-electrode analysis showed that the source of the gamma activity could be statistically
29 dissociated from the lower-frequency response.

30 These findings are in accordance with separate functional roles for the activity in each
31 frequency band, and provide evidence that the oscillatory activity that underpins the auditory
32 evoked response may contain important information about the physiological basis of the
33 macroscopic signals recorded by MEG in response to auditory stimulation.

Keywords

37 beamformer, cortex, magnetoencephalography, oscillations

38

39 1 Introduction

40 The auditory N1, termed the N1m in MEG data, is a large evoked response elicited by the
41 onset of a sound and originating in auditory cortex (Näätänen & Picton, 1987). It is relatively slow
42 and prolonged, consisting of a series of waves between about 75 and 120 ms following stimulation
43 (see Figure 1). Less frequently-reported is the auditory evoked-gamma response, which is typically
44 10-15 times smaller than the N1 (Jacobson & Fitzgerald, 1997). Sometimes observed as 'notching'
45 superimposed on the slow waves of the N1, it is most easily viewed in data that has been high-pass
46 filtered to exclude frequencies below 30 Hz (Jacobson & Fitzgerald, 1997; Pantev, 1995). Dipole-
47 modelling (Pantev, 1995) and cortical surface recordings (Jacobson & Henderson, 1998) have
48 suggested that the auditory evoked-gamma response originates from a separate source to the slower
49 N1 and may therefore be functionally different. The objective of this study was to characterize the
50 spatio-temporal characteristics of the evoked oscillatory activity during auditory processing.

51
52 Gamma-band activity, here classified as synchronous neuronal oscillatory activity at 30 - 70 Hz,
53 results from the coordinated interaction between excitatory and inhibitory neurons (Bartos, Vida, &
54 Jonas, 2007) and is functionally widespread in the brain. It is predominant during high attentional
55 states, and induced (i.e. stimulus-related but not time-locked) gamma band changes in particular
56 have been implicated in high-level cortical processes such as sensory perception (Engel & Singer,
57 2001; Gray & Singer, 1989; Singer, 1993), learning and memory processes (Buzsáki & Chrobak, 1995;
58 Lisman & Idiart, 1995; Lisman, 1999), memory storage and retrieval (Colgin & Moser, 2010) as well as
59 object recognition and language perception (Crone, Boatman, Gordon, & Hao, 2001; Kaiser, Hertrich,
60 Ackermann, Mathiak, & Lutzenberger, 2005). Evoked, rather than induced, gamma activity is most
61 commonly observed in auditory cortex. The steady-state evoked response to an amplitude-
62 modulated tone is strongest when the rate of modulation falls in the gamma band (40 Hz; e.g. Rees,
63 Green, & Kay, 1986; Ross et al., 2000), indicating that auditory cortical networks are optimised to
64 oscillate in this range. However this is a *driven* response and most likely differs mechanistically from

65 the brief burst of intrinsic gamma oscillations that accompanies the N1m. The evoked gamma activity
66 that follows a transient auditory stimulus such as a tone or click is known to be affected in terms of
67 both amplitude and connectivity patterns by task conditions (e.g. Mulert et al., 2007, Polomac et al.,
68 2015), implying that it has functional significance.

69 Hierarchical models of auditory cortical processing suggest that the holistic perception of
70 auditory 'objects' (acoustic events or sources; see Griffiths & Warren 2004) emerges from serial
71 processing in a sequence of brain areas beginning with those lying within Heschl's gyrus, and
72 progressing to areas in planum temporale and STS where more complex analysis of stimulus features
73 takes place (Kumar, Stephan, Warren, Friston, & Griffiths, 2007). Such models underline the need for
74 effective communication between sub-regions within Heschl's gyrus, planum temporale, and beyond,
75 as well as the dynamic recruitment of neurons within these sub-regions to form local networks.
76 Oscillatory dynamics, widely implicated in communication within networks (Wang, 2010) can
77 therefore be hypothesised to play a central role in facilitating and controlling the communication
78 between regions within auditory cortex. For example, within auditory cortex, persistent gamma
79 oscillations have been observed in superficial layers (Traub, Bibbig, LeBeau, Cunningham, &
80 Whittington, 2005) while slower oscillations, such as those in the beta-band or lower, which can
81 synchronise over longer delays, are thought to enable communication between regions that are
82 spatially more separated (Kopell, Ermentrout, Whittington, & Traub, 2000). If patterns of oscillatory
83 activity can be effectively localised and distinguished at the macroscopic level, then this will provide
84 important opportunities to further explore the cortical pathways involved in auditory perception.

85 An early MEG study using the single-dipole modelling approach established that this
86 response originates in supra-temporal auditory cortex, adjacent to but 'deeper' than the N1m
87 response (Pantev et al., 1991). Important recent developments in MEG data analysis, using whole-
88 head MEG systems with dense coverage, have provided new methods, such as beamformers
89 (Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; Vrba & Robinson, 2001), that are particularly
90 suited to the study of brain responses that are specifically defined in terms of their frequency

91 characteristics (like gamma-band activity). Beamformers provide several additional benefits over
92 more traditional dipole-fitting techniques, especially the absence of any need for *a-priori*
93 assumptions about the number of sources (van Veen et al. 1997), and their ability to significantly
94 enhance the signal-to-noise ratio of the data (Adjamian et al., 2009). The use of such techniques
95 therefore allows for a more detailed characterisation of the low-amplitude evoked-gamma response,
96 and should potentiate our understanding of its functional role. In this study, we used beamformer
97 analysis of MEG data to characterize the spatio-temporal properties of the oscillatory changes that
98 underpin the gamma-band and lower-frequency components of the auditory evoked response, with
99 the objective of gaining insight into their functional relation within auditory cortex.

100 **2 Materials and Methods**

101 2.1 Participants

102 11 adults (7 females; age-range 26-71 years), with no reported neurological or audiological problems,
103 took part in the study. Participants were recruited from an ad-hoc population of university staff and
104 graduate students. The study was conducted in accordance with the Declaration of Helsinki and with
105 the consent of the local Ethics committee.

106 2.2 Stimuli

107 The stimuli were a train of 200 acoustic clicks with an average inter-stimulus interval of 1200 ms,
108 randomly jittered by plus or minus 200 ms and presented using a PC running Presentation® software
109 (version 0.7, www.neurobs.com). These were delivered monaurally to the left and right ears in
110 separate recordings (in counterbalanced order across participants), through echoless plastic tubing
111 and foam ear-tips at a comfortable, calibrated, 50dB hearing level.

112 2.3 MEG data collection

113 Data were recorded using a 275-channel whole-head CTF MEG system (CTF Systems, Port Coquitlam,
114 Canada), while participants were seated with their eyes open in a dimly lit magnetically shielded
115 room, watching a silent video to maintain alertness. The measurements for this study took less than
116 5 minutes and formed part of a longer recording session involving auditory measurements for other

117 studies. MEG data were recorded using synthetic third-order gradiometers (Vrba et al., 1999),
118 sampled at 600 Hz with an anti-aliasing filter of 300 Hz, power-line filtered, and subdivided into
119 epochs starting 500 ms before each click to 500 ms following each click. Each epoch was baseline-
120 corrected by the mean amplitude of the 500-ms pre-stimulus period. The epochs were stringently
121 screened visually for physiological artefacts such as those arising from eye-blinks and muscle activity,
122 resulting in the removal of on average 32 epochs per dataset.

123 Source modelling was achieved by using an event-related beamformer (Cheyne, Bostan,
124 Gaetz, & Pang, 2007). MEG data were spatially coregistered with the individual's structural MRI
125 using a modification of the surface-matching method described by Adjamian et al (2004), and a
126 multi-sphere head model (Huang, Mosher, & Leahy, 1999) was derived from each participant's outer
127 skull surface. Noise-normalised weights were computed from the un-averaged data, using a time
128 window from 0 to 200 ms post-trigger, for two separate frequency bands: 4-30 Hz ('theta-to-beta')
129 and 30-70 Hz ('gamma'). While power estimates for the lowest frequencies may have been sub-
130 optimal due to the use of brief time windows for the covariance estimation (Brookes et al., 2008),
131 our inclusion of the theta-band allowed us to capture some of the slower components associated
132 with the traditionally-defined N1m response. The weights were applied to the averaged data, which
133 had been filtered into the same frequency band, for the time-points of interest – the largest peak of
134 the auditory evoked-gamma response and the N1m for each individual and hemisphere, to yield a
135 volumetric image.

136 The co-ordinates of peak voxels were transformed to Talairach co-ordinates by manual
137 identification of key landmarks (the anterior and posterior commissures; Talairach & Tournoux, 1988)
138 using MRI3dX software (v. 7.63) to enable comparison between individuals. Activations were
139 accepted if they fell broadly within, or close to, the superior surface of the temporal lobe, near or
140 posterior to Heschl's gyrus. They had to fall between co-ordinates of -10 and 30 in the Z-direction
141 (inferior-superior) and 0 and -60 mm in the X-direction (anterior-posterior), but were not restricted
142 in the Y-direction except that they had to fall within the expected hemisphere. They also had to fall

143 within the 5 maximal peaks obtained by the analysis (we allowed the rank of the peak to vary
144 because, although we expected auditory cortical activation to be the most significant activity
145 observed in this paradigm, localisable artefacts, other task-related activity, or spurious activations
146 (Quraan & Cheyne, 2010) could also cause peaks in the image, such that we would have missed
147 genuine activation if we had only selected the main peak). The pseudo-Z score for each accepted
148 peak voxel was also recorded. Full-width half-maximum (FWHM) analyses of peak smoothness were
149 computed according to the method described by Barnes and Hillebrand (2003).

150

151 2.4 Virtual Electrode (VE) Analysis

152 VE time series were constructed (Hillebrand et al., 2005; Robinson & Vrba, 1999) to allow
153 analysis of the spectro-temporal properties of evoked activity at the sources identified in the
154 volumetric images, using the co-ordinates of each individual's response. The previously computed
155 noise-normalised weights were multiplied by the averaged, unfiltered sensor data to produce virtual
156 electrode time series. Time-frequency spectrograms were created using Morlet wavelets with a
157 width of 7 cycles. For comparison of evoked response time series in the virtual electrode data at
158 each cortical location of interest, the time series were both filtered into the theta-to-beta band and,
159 separately, the gamma band. Each was then individually scaled relative to one standard deviation of
160 the evoked-response time series in its pre-stimulus baseline period (i.e., 1 standard deviation of
161 pooled sample-points). This scaling allowed comparison of evoked response morphology between
162 source models, despite any differences in overall signal amplitude. Group means and standard
163 deviations were then computed for each filtered, standardised, time series at each cortical location.

164

165 2.5 Anatomical Localisation

166 The mean coordinates for gamma-band and theta-to-beta responses were examined to
167 determine where these responses were localised in auditory cortex. The mean Talairach coordinates
168 defined with MRI3dX were converted to MNI space using the GingerALE MNI2Tal tool (Laird et al.,

169 2010; Lancaster et al., 2007). These coordinates were then displayed with primary auditory cortex
170 probabilistic maps for the medial to lateral cytoarchitectonic regions Te1.1, Te1.0, and Te1.2
171 (Morosan et al., 2001). This qualitative examination allowed for further characterization of the
172 spatial separation between the gamma and theta-to-beta responses.

173

174 **3 Results**

175 3.1 Sensor Data: Relative amplitude and latency in the gamma and theta-to-beta bands.

176 Figure 1 shows example data from a sensor over the temporal lobe, filtered between 1 and
177 30 Hz illustrating the N1m response (Fig. 1a), and separately between 30 and 70-Hz illustrating the
178 evoked-gamma response (Fig. 1b). The approximately five-fold difference in amplitude between the
179 responses in each filter-band can be seen by comparing values on the ordinate axes. Table 1 shows
180 the means with standard deviations for the latencies of the peak of each response observed in the
181 sensor data, along with the number of participants showing a discernible response upon which these
182 data are based. For each ear of stimulation, 10 of the 11 participants showed a clear N1m response
183 in the sensor data for the hemisphere contralateral to stimulation (i.e. one did not show a
184 contralateral response for left-ear stimulation, and a different participant did not for right-ear
185 stimulation). The two participants who did not show an N1m response did both show activation in
186 the gamma band. Contralateral gamma-band responses, occurring around 80 ms, were discernible in
187 8 participants for stimulation in each ear (5 cases with bilateral responses). A subset of participants
188 also showed N1m or gamma-band responses in the hemisphere ipsilateral to stimulation (also
189 shown in Table 1). There were no statistically significant differences between hemispheres in
190 response latency for contralateral or ipsilateral responses, or between contralateral and ipsilateral
191 responses within hemispheres (Wilcoxon ranked pairs, $p > 0.05$).

192

193 3.2 Source Models: Spatial Dissociation of Responses

194 There were 10 acceptable contralateral and 4 ipsilateral theta-to-beta sources for left ear
195 stimulation; and 9 contralateral, 8 ipsilateral for right-ear stimulation. A subset of the participants
196 yielded an acceptable source in the gamma band which fell within our region of interest: 6
197 contralateral and 5 ipsilateral following left-ear stimulation, and 8 contralateral and 7 ipsilateral
198 following right-ear stimulation. The following anatomical descriptions and statistical comparisons
199 focus on the contralateral responses, although data for the ipsilateral responses are presented in
200 Table 2 and Figure 2.

201 In the left hemisphere, the mean gamma response was observed on the crown of Heschl's
202 gyrus with at least a 50% probability of falling within cytoarchitectonic region Te1.0 (MNI: -49, -17,
203 8). In contrast, the theta-to-beta response was more lateral than the gamma response and localised
204 to the boundary of regions Te1.2 and Te1.0 (MNI: -58, -20, 13). The right hemisphere mean gamma
205 and theta-to-beta responses were again spatially separated, but both shifted more medially. The
206 mean gamma response was observed in the superior temporal gyrus, inferior to the boundaries
207 Te1.1 and Te1.0 (MNI: 50, -23, 1). The more lateral theta-to-beta response was observed in the
208 planum temporale and at the boundary of Te1.1 and Te1.0 regions (MNI: 53, -23, 9).

209 The spatial variability of the left and right hemisphere localisations, as well as their relative
210 spatial positions, is demonstrated in Figure 2. The 95 % confidence intervals for each mean response
211 have the tendency to be more ovoid in the anterior-posterior (Y) and superior-inferior (Z) directions,
212 compared to the medial-lateral (X) direction. The more consistent localisation in the medial-lateral
213 direction is consistent with the significant difference in the X location between gamma and theta-to-
214 beta responses (across both hemispheres, paired t-test of the gamma vs theta-to-beta X location: $t =$
215 4.36 , $p < 0.001$), but not for the Y and Z locations. Thus, the theta-to-beta responses lie consistently
216 lateral to those in the gamma band.

217

218 3.3 Virtual electrode analysis: Spatiotemporal characteristics of VE time series.

219 An analysis of the virtual electrode time series was conducted in order to further explore the
220 observation of a spatial separation between responses in the gamma band and the N1m (theta-to-
221 beta) response in the left hemisphere. We reconstructed virtual electrodes for left-hemisphere
222 sources from right-ear stimulation in each frequency band for the 7 participants who showed
223 contralateral activations for right-ear stimulation (i.e. left-hemisphere responses) in both the theta-
224 to-beta and gamma bands, and for right-hemisphere sources for the five participants who showed
225 contralateral activations in both bands for left-ear stimulation (i.e. right-hemisphere responses). The
226 volumetric event-related beamformer localisation relies on filtering both the un-averaged data to
227 produce the weights and the average data to represent the results in a frequency band of interest.
228 However activity falling outside this frequency-band of interest may co-occur at the same location,
229 and we can visualise this by applying the same weights to an average that has not been filtered, or
230 has been filtered in a different frequency band, thereby revealing whether a single location
231 contributes to activity in multiple frequency bands.

232 Figure 3 shows the data for right-ear stimulation: Figs 3a and 3b show group-averaged
233 spectrograms of the evoked activity at the peak sources for theta-to-beta and gamma activity in the
234 left hemisphere, respectively. A burst of spectral power in each frequency band is clearly visible at
235 both locations, though the relative strength of the activity in the gamma band (i.e. the activity
236 localised by the beamformer) is slightly greater at the gamma location (Fig. 3b) and vice-versa.
237 Figures 3c and 3d compare between the evoked responses at the location of the gamma and the
238 theta-to-beta virtual electrodes. In Fig 3c, both the VE time series are filtered in the theta-to-beta
239 frequency band (4-30 Hz), standardised and averaged across subjects. A clear tri-phasic evoked
240 response is observed for both locations, i.e., for both the source of the peak gamma and the source
241 of the peak theta-to-beta activity, which is consistent with the traditionally-defined N1m shown in
242 Figure 1a. The overall standardised amplitude is larger at the source of the gamma activity (despite
243 the VE having been identified as the strongest source of activity in the theta-to-beta band), though
244 standard error-bars are large, and overlap. The trend towards a difference in amplitude at each

245 location is likely due to increased inter-individual differences in response timing at the theta-to-beta
246 location (not shown in Figures). Nonparametric Wilcoxon tests confirm that there is no significant
247 difference between the amplitudes at the maxima of the second and third waves ($W(6) = 7$, $p >$
248 0.05). A small but significant difference (i.e. with greater amplitude at the gamma source) is
249 observed at the earliest wave in the average VE time series, which occurs at around 80 ms ($W(6) =$
250 2 , $p = 0.047$). Figure 3d shows the same VE time series, now filtered in the gamma band (30-70 Hz).
251 A burst of evoked gamma occurs in each location but the amplitude is significantly greater in the
252 virtual electrodes obtained from the maximum of gamma-band activity than in those for the theta-
253 to-beta source ($W(6) = 0$, $p = 0.016$). Therefore, the gamma-band response amplitude is greater at
254 its peak source than at the peak of the lower-frequency activity, whereas the amplitude of theta-to-
255 beta activity is statistically equivalent at both locations, except in its earliest phase. A very similar
256 pattern of results was found for the activations resulting from left-ear stimulation, shown in Figures
257 3f and 3g. This only differs from the left-hemisphere data in the overlap between error bars at the
258 80-ms peak, although this analysis is based on only 5 participants. Indeed there were insufficient
259 samples (providing only 4 degrees of freedom) to formally test differences in amplitude for statistical
260 significance at the 0.05 alpha level. A further analysis of the FWHM of the event-related
261 beamformer peaks (Barnes & Hillebrand, 2003) suggested an average of 17 mm (range 12-27) and 20
262 mm (range 13-20) for the theta-to-beta and gamma peaks respectively (no significant difference,
263 Wilcoxon ranked pairs: $p > 0.05$). This suggested that although the peaks of sources can be
264 distinguished appropriately based on the 5mm voxel grid used here, the uncertainty in the
265 reconstructed source locations is such that the possibility of a degree of overlap between the
266 sources cannot be excluded.

267 Reviewing sensor data, we observed that all seven of the participants in our left-hemisphere
268 analysis who showed gamma activity also showed a small wave around 80 ms in the theta-to-beta
269 band, although in one case this merged into the N1m. The mean (and standard deviation) latency of
270 this response for left-ear stimulation was 72 ms (5 ms; $n = 7$) in the contralateral hemisphere and 77

271 ms (8 ms; n = 5) in the ipsilateral hemisphere. The mean (and standard deviation) latency of the
272 response for right-ear stimulation was 81 ms (10 ms; n = 6) in the contralateral hemisphere and 80
273 ms (9 ms; n = 6) in the ipsilateral hemisphere. These latencies did not differ significantly from those
274 for the gamma response shown in Table 1 (Wilcoxon ranked pairs, all $p > 0.1$). Yet they consistently
275 failed to yield acceptable ER-beamformer activations in the theta-to-beta band, perhaps because of
276 their relatively small amplitude, so their sources could not be modelled further. Figure 3e shows the
277 Hilbert envelope of the gamma-band activity, and the time series of the theta-to-beta activity, both
278 at the source of the peak gamma-band response. It can be seen that the rise in amplitude of the
279 gamma response coincides with, or just precedes, the rise in amplitude of the lower-frequency
280 response. However the phase-relationship between gamma and theta-to-beta activity was not
281 robust when examining time series from individual virtual electrodes: in some cases the gamma
282 preceded the rise of the low-frequency response and in other cases, *vice-versa*.

283 **4 Discussion**

284 Our data show that patterns of spectral power in specific frequency bands constitute an
285 important distinguishing feature of the different components of the auditory evoked response, and
286 localise to different regions of auditory cortex. In our volumetric images, the locations of peak
287 gamma and peak theta-to-beta activity were spatially distinct in the hemisphere contralateral to
288 stimulation, with the gamma responses falling more medial than the theta-to-beta responses (Figure
289 2). Our results also indicate that the activity in the theta-to-beta band is spatially widespread.
290 Conversely, the gamma-band response appears to be more focal, and is significantly smaller at the
291 location of the peak low-frequency response than at the location of the peak gamma response (Figs.
292 3c and 3d). These observations show that gamma-band response and the traditionally-defined N1m
293 have temporally distinct onsets that correspond spatially with a hierarchical processing stream
294 through auditory cortex.

295

296 4.1 Spatial Dissociation of Responses

297 The average localisation for both the gamma-band response and the theta-to-beta
298 responses fell within or close to Heschl's gyrus. Importantly, gamma-band activity occurred in a
299 significantly more medial position than theta-to-beta band activity. Primary auditory cortex has
300 been described as having a set of core regions with at least 3 primary-like fields along the axis of the
301 gyrus, with information flowing from medial to more lateral locations (Hackett, Preuss, & Kaas, 2001;
302 Hackett, 2011). The mean localisations roughly corresponded to different cytoarchitectonic regions,
303 suggesting that there are unique generators of gamma and theta-to-beta activity that are spatially
304 distinct (although possibly overlapping) and may reflect stages of processing through the auditory
305 system; this interpretation is also supported by the data in Figure 3d which show a significant
306 difference between gamma-band amplitude at each source.

307 Gamma responses were localised to medial-lateral planes where Heschl's gyrus and the
308 planum temporale are clearly observable. This location, particularly in the left hemisphere,
309 corresponds to cytoarchitectonic region Te1.0 where there is a relatively thicker layer IV, i.e.
310 receiving more thalamic input, than in the more medial Te1.1 and more lateral Te1.2 (Morosan et
311 al., 2001). While cortex can generate gamma activity independently of thalamic input (Barth &
312 MacDonald, 1996; Whittington, Traub, & Jefferys, 1995), the correspondence with a
313 cytoarchitectonic region that receives relatively greater thalamic input than the other Te regions is
314 consistent with suggestions that thalamic activity can also impact gamma activity (Barth &
315 MacDonald, 1996; Metherate & Cruikshank, 1999). We also observed a small amount of gamma
316 activity at the peak of the theta-to-beta activity, which could result from signal leakage in the
317 beamformer model, or from overlapping sources – but alternatively it could have a neuronal origin.
318 Chattering neurons in superficial layers of visual cortex can also generate gamma activity (Gray &
319 McCormick, 1996) and it may be these neurons in auditory cortex that propagate gamma activity
320 through auditory cortex (Metherate & Cruikshank, 1999). Future studies could further explore the
321 independence of the gamma band responses at the two locations using modified beamformer
322 approaches (Hui et al., 2010; Diwakar et al., 2011; Brookes et al., 2007).

323 Theta-to-beta responses were localised to more lateral temporal lobe regions, where the
324 Heschl's gyrus morphology is highly variable across cases (Leonard, Puranik, Kuldau, & Lombardino,
325 1998), than the more medial primary gamma responses. The most probable cytoarchitectonic
326 regions for theta-to-beta responses varied between hemispheres. In the left hemisphere, the
327 response corresponded to cytoarchitectonic region Te1.2, where there is a relatively thicker layer III
328 compared to Te1.0 and Te1.1 (Morosan et al., 2001). Layer II/III supragranular neurons demonstrate
329 robust theta- and gamma-band activity in response to clicks (Lakatos, Chen, O'Connell, Mills, &
330 Schroeder, 2007). We are cautious about interpreting the significance of localisation to Te1.2 in the
331 left hemisphere though, because the right hemisphere theta-to-beta response was more likely in
332 Te1.0. Moreover, relative layer thickness may not be the only, or most important, factor that
333 determines the location of the peak gamma and theta-to-beta responses.

334 Cautious interpretation of the localisations is also warranted based on the high superior-
335 inferior and anterior-posterior variability compared to the medial-lateral variability. The more lateral
336 theta-to-beta responses may be particularly impacted by individual differences in sulcal/gyral
337 morphology, as this will result in individual differences in the orientation of neurons with respect to
338 the sensors and subsequently in localisation accuracy (Hillebrand & Barnes, 2002). Indeed, Heschl's
339 gyrus morphology is increasingly variable across cases with increasingly lateral positions of the
340 superior temporal gyrus (Leonard et al., 1998) and Heschl's gyrus morphology has been related to
341 the magnitude of MEG responses to amplitude modulated tones (Schneider et al., 2002). Future
342 studies with larger sample sizes may show that individual variance in Heschl's gyrus and Sylvian
343 fissure morphology impacts the localisation of gamma and theta-to-beta responses. Individual
344 differences in anatomy and potential registration error are less problematic for comparing the
345 relative position of gamma and theta-to-beta responses using a within subjects design. Thus, we can
346 more reliably conclude that theta-to-beta activity occurs laterally to the primary gamma responses
347 to click stimuli.

348

349 4.2 Functional significance of activity in the gamma-band and theta-to-beta band

350 The spatial and temporal separation between the gamma-band response at 80-ms and the
351 traditionally-defined N1m (i.e., the later component of the theta-to-beta response) is consistent with
352 a functional distinction between their roles in the auditory responses. This result further
353 strengthens an argument that MEG can be used to observe the processing of the clicks from medial
354 to more lateral locations in auditory cortex.

355 Although the gamma activity described here is relatively late compared to the first signals
356 arriving at the cortex following stimulation, which occur at around 20 ms (Lütkenhöner et al., 2003),
357 evidence from intracortical recordings suggests that this frequency band is typically associated with
358 bottom-up processes (Fontolan, Morillon, Liegeois-Chauvel, & Giraud, 2014), and its role in auditory
359 thalamocortical coherence has previously been suggested (Ribary et al., 1991). While all areas in the
360 core of Heschl's gyrus receive thalamic inputs, the peaks of our MEG signals will be centred at the
361 spatial location where the bulk of activity originates. Again, the gamma response was more likely in
362 Te1.0 where there is considerable thalamic input based on its relatively expanded layer IV.

363 Activity in the theta-to-beta band localises to more lateral areas of auditory cortex (Figure 2)
364 and persists for longer than the gamma response (Figure 3), suggesting a role for this lower-
365 frequency activity either in the flow of information along the auditory core and beyond, or top-down
366 processes flowing towards A1. Evidence from intracortical depth recordings in A1 and auditory
367 association cortex during speech stimuli has supported a functional distinction between gamma-
368 band activity, reflecting bottom-up processes, and activity in lower frequency bands as a signature of
369 top-down processing (Fontolan et al., 2014).

370 At the physiological level, oscillatory frequency will typically demonstrate an inverse
371 relationship with the extent of neuronal recruitment (Buzsáki, 2006), possibly because when a
372 rhythm is fast, only small groups of neurons can follow due to the limitations of conduction and
373 synaptic delays. Our time series data imply that the source of the gamma-band activity may indeed
374 be more focal than the source of the theta-to-beta activity. Although the FWHM analysis, which

375 showed no significant difference between the spatial extents of the beamformer reconstructions,
376 does not seem to support this conclusion, it is important to realise that the extent of a peak in a
377 beamformer image does not relate one-to-one to source extent. Indeed, very accurate models of
378 cortical surface information are required for detailed assessment of source extent (Hillebrand &
379 Barnes 2011)). Our analysis of virtual electrode timeseries data, along with the evidence from our
380 confidence intervals, provide strong evidence for physiological dissociation between activity at these
381 different sources. This provides a motivation for future detailed studies of MEG responses in
382 auditory cortex, using beamformer methods with much higher numbers of trials to improve SNR and
383 higher voxel resolution to allow finer dissociation between sources. Although the number of trials
384 used in this study significantly exceeds that typically required to obtain an N1-P2 response in clinical
385 electrophysiology (typically about 40-60 trials), it is possible that the accuracy and spatial selectivity
386 of source localisations, as well as the consistency of timeseries data, would improve with greater
387 numbers of trials. Further, while we did not specifically look for *induced* gamma activity in our
388 analyses, none was observed – however. However with a significantly increased trial-count this may
389 have emerged in the plots, or been localisable by using a standard dual-state (not event-related)
390 beamformer analysis.

391

392 On average, the rise in gamma activity for the VEs was temporally co-incident with the rise
393 of the 80-ms response in the lower frequency band, although this observation was not robust at the
394 single-subject level, perhaps because of a lack of statistical power in the VE data. Coupling between
395 induced theta rhythms and the envelope of bursting induced gamma activity has been well
396 described in other brain areas (Canolty & Knight, 2010). Another way in which the two rhythms
397 might be functionally related is through a common mechanism underpinning the generation of the
398 evoked response. The ‘Firefly model’ (Burgess, 2012) provides a framework based on the phase-
399 alignment of intrinsic oscillatory activity, which occurs through a slowing of rhythms that cascades
400 from high to low frequencies. Thus, stimulus-related changes in the gamma band would be

401 expected to precede changes in lower frequencies. Individual differences in our data make it
402 impossible to draw firm conclusions about the potential relationship between activity in these two
403 frequency bands. Most notable was the fact that our dataset included two people who showed an
404 evoked-gamma response in the absence of a traditionally-defined N1m response. This supports the
405 view that the responses in the two frequency bands are functionally separate, although individual
406 differences in the orientation of the respective neural generators could also account for this
407 observation.

408

409 **5 Conclusions**

410 In summary, these data provide evidence that the oscillatory activity that underpins the
411 auditory evoked response may contain important information about the physiological basis of the
412 macroscopic signals recorded by MEG in response to auditory stimulation. Functional and spatial
413 dissociations between activity in different frequency bands provide an opportunity to explore the
414 dynamics of auditory processing and significantly supplement the information provided by
415 traditional evoked response methods. More broadly, the results provide a richer understanding of
416 auditory evoked responses that may be leveraged to understand where and when stimulus
417 properties are typically processed and why people experience auditory processing difficulties.

418

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423

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- 581
- 582

583

584 **Table 1**

Frequency	Left Ear Stimulation		Right Ear Stimulation	
Band	Contralateral Response	Ipsilateral Response	Contralateral Response	Ipsilateral Response
N1m	115 (12) n = 10	113 (10) n = 9	111 (11) n = 10	113 (15) n = 6
Gamma	79 (8) n = 8	78 (7) n = 6	76 (8) n = 8	77 (10) n = 5

585

586 Table 1 Legend: Mean (and standard deviation) latencies of the peak evoked responses, in ms, for
 587 the N1m and gamma-band responses. There were no significant differences between contralateral
 588 and ipsilateral latencies (Wilcoxon ranked pairs, $p > 0.05$).

589

590

591 **Table 2: Pseudo Z values**

Frequency Band	Left Ear Stimulation		Right Ear Stimulation	
	Contralateral Response	Ipsilateral Response	Contralateral Response	Ipsilateral Response
Theta-to-Beta (4-30 Hz)	16.2 (6.2) n = 10	6.4 (3.2) n = 4	13.0 (4.0) n = 9	10.2 (1.9) n = 7
Gamma (30-70 Hz)	14.2 (4.3) n = 6	9.2 (3.1) n = 5	12.3 (5.6) n = 8	11.6 (3.0) n = 7

592 **Table 2: legend**

593 Mean and standard deviation pseudo-Z values in the contralateral and ipsilateral hemispheres, in the
 594 theta-to-beta and gamma frequency bands. Despite a trend for the ipsilateral pseudo-Z values to be
 595 smaller, this was not statistically significant (Wilcoxon ranked pairs, $p > 0.05$).

596

597

598 Figure Legends

599

600 Figure 1

601 Figure 1 shows example evoked responses, taken from one MEG sensor located over the temporal
602 lobe contralateral to stimulation. In Fig. 1a, the response is bandpass-filtered between 1 and 30 Hz,
603 and in Fig. 1b the response is filtered between 30 and 70 Hz.

604

605 Figure 2

606 **Figures 2a and 2b** show mean and 95% confidence intervals for the ER beamformer peaks in the
607 theta-to-beta (dark blue) and gamma (light blue) frequency bands, plotted over the outline of
608 auditory cortex (Heschl's gyrus and planum temporale), traced from the 12mm slice of the Talairach
609 brain (Talairach & Tournoux 1988). Fig. 2a shows contralateral, i.e., right-hemisphere (n = 8 for each
610 frequency band) and ipsilateral activity (n = 7 for each band) resulting from left-ear stimulation,
611 while Fig. 2b shows contralateral (theta-to-beta, n = 10; gamma, n = 5) and ipsilateral (n = 4 for both
612 frequency bands) activity resulting from right-ear stimulation.

613

614 Figure 3

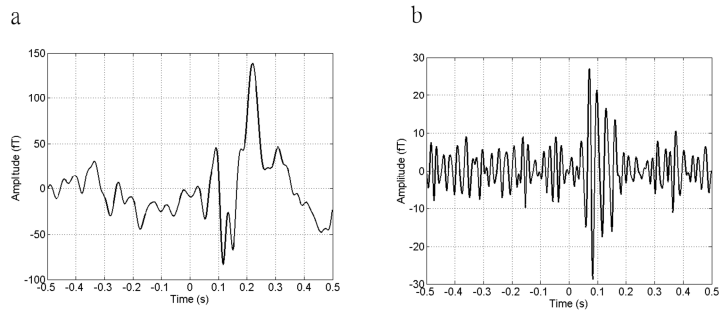
615 Figure 3 shows virtual electrode data for contralateral responses resulting from right-ear
616 stimulation, for the 7 participants who showed a response in both frequency bands. Figs. 3a and 3b
617 show wavelet spectrograms of activity at the source of the theta-to-beta activity and gamma activity
618 respectively. Figs. 3c and 3d show evoked response time series at the sources of the theta-to-beta
619 activity and gamma activity, filtered in the low frequency band (3c) and gamma-band (3d),
620 respectively. These are scaled as a function of 1 standard deviation of pre-stimulus activity in each
621 individual and averaged. Error bars show standard deviations of the peak amplitudes. Figure 3e
622 shows the relative timing of the activity in each frequency at the location of the peak gamma
623 response. The Hilbert envelope of the gamma activity, shown in red, is plotted with the slow (theta-

624 to-beta) response at the same location in Figure 3e. Figures 3f and 3g show the similar plots to 3c

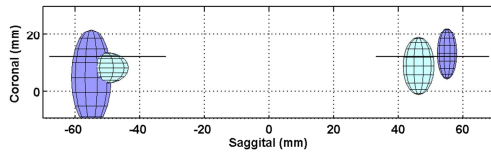
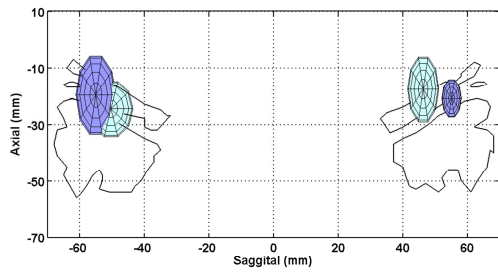
625 and 3d, using the data from left ear stimulation and sources in the right hemisphere.

626

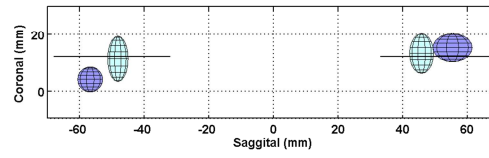
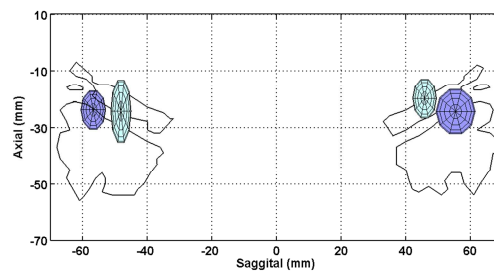
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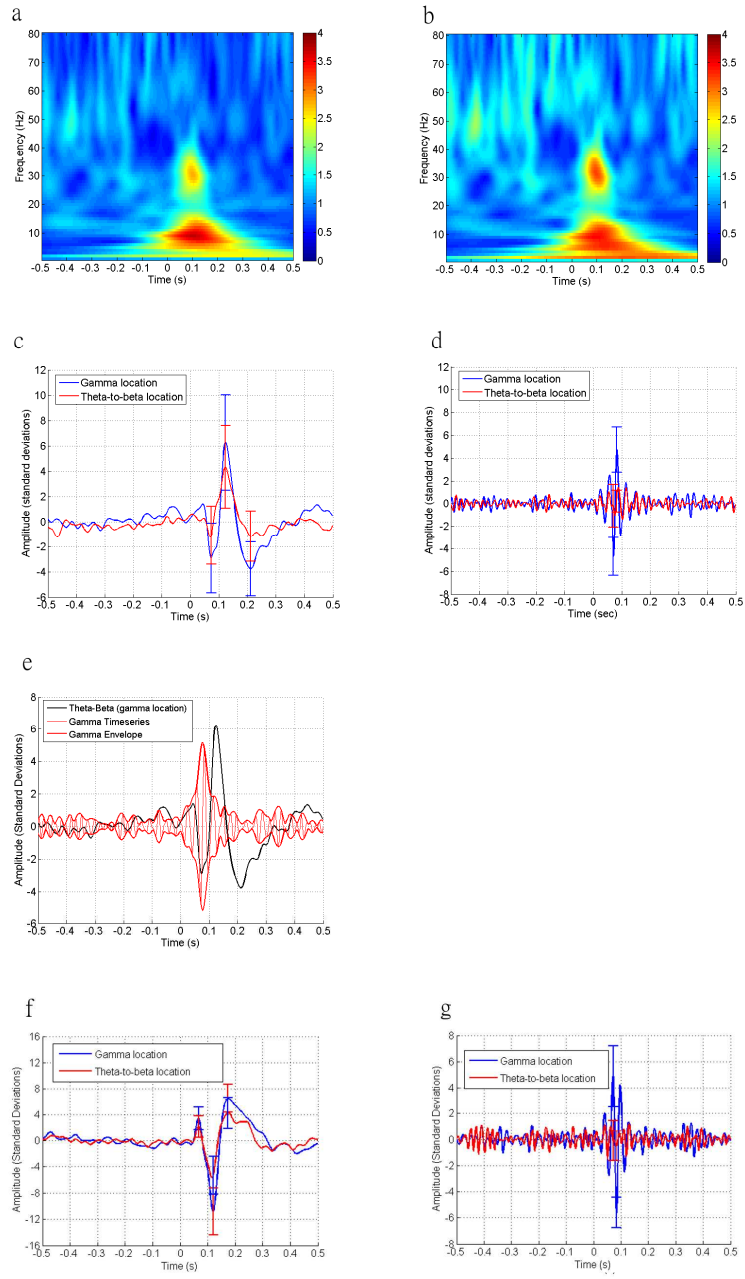


a. Left ear stimulation



b. Right ear stimulation





Highlights

- We compare the auditory cortical N1m and evoked gamma responses using MEG
- Gamma-band activity originates more medially in auditory cortex than the N1m
- Gamma activity is earlier and spatially distinct from N1m responses
- Data are consistent with separate origins and functional roles of these responses