

Hexadirectional modulation of high-frequency electrophysiological activity in the human anterior medial temporal lobe maps visual space

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1 Current Biology. Report.

2

3 Title: **Hexadirectional modulation of high-frequency electrophysiological activity in the human**
4 **anterior medial temporal lobe maps visual space**

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22 **Summary**

23 Grid cells are one of the core building blocks of spatial navigation [1]. Single cell recordings of grid cells in
24 the rodent entorhinal cortex revealed hexagonal coding of the local environment during spatial navigation
25 [1]. Grid-like activity has also been identified in human single cell recordings during virtual navigation [2].
26 Human fMRI studies further provide evidence that grid-like signals are also accessible on a macroscopic
27 level [3-7]. Studies in both non-human primates [8] and humans [9, 10] suggest that grid-like coding in the
28 entorhinal cortex generalizes beyond spatial navigation during locomotion, providing evidence for grid-
29 like mapping of visual space during visual exploration - akin to the grid cell positional code in rodents
30 during spatial navigation. However, electrophysiological correlates of the grid-code in humans remain
31 unknown. Here, we provide evidence for grid-like, hexadirectional coding of visual space by human high
32 frequency activity, based on two independent data sets: non-invasive magnetoencephalography (MEG) in
33 healthy subjects and entorhinal intracranial EEG recordings in an epileptic patient. Both data sets
34 consistently show a hexadirectional modulation of broadband high frequency activity (60-120 Hz). Our
35 findings provide first evidence for a grid-like MEG signal, indicating that the human entorhinal cortex
36 codes visual space in a grid-like manner [8-10] and support the view that grid-coding generalizes beyond
37 environmental mapping during locomotion [4-6, 11]. Due to its millisecond accuracy, MEG recordings
38 allow to link grid-like activity to epochs during relevant behavior, thereby opening up the possibility for
39 new MEG-based investigations of grid coding at high temporal resolution.

40

41 **Results**

42 The present study set out to investigate the electrophysiological basis of grid-like, hexadirectional coding
43 during visual exploration in humans, by simultaneously recording MEG and eye-tracking data from 35
44 healthy participants during free viewing of natural scenes (Fig. 1a), and simultaneously recording
45 intracranial EEG and eye-tracking data with depth electrodes in the entorhinal cortex of one epilepsy
46 patient (Fig. S1). Although the exact physiology of the broadband high frequency activity (BHA) remains
47 to be discovered, it has been shown to correlate with local neural activity [12-15]. Building on this and
48 other work demonstrating high frequency activity in the entorhinal cortex of behaving rodents [16], we
49 hypothesized to find a grid-like modulation of neuromagnetic BHA in the anterior medial temporal lobe
50 (MTL; Fig. 1b) and sought to verify the MEG findings in the intracranial recordings.

51

52 **Grid-like modulation of source-localized broadband high frequency MEG data maps visual space**

53 MEG data were aligned to saccade onsets (Fig. 1a) and BHA power (60-120 Hz) source-localized to the
54 anterior MTL (Fig. 1b), was extracted during saccadic eye movements. We used a recently optimized MTL
55 source reconstruction method [17], extending prior MEG work localizing MTL activity [18-22]. Applying a
56 quadrature filter approach [3], we estimated the phase of hexadirectional activity as a function of saccade
57 direction (putative 'grid orientation') and subsequently quantified BHA power aligned and misaligned to
58 the main grid axis, in a two-fold cross-validation design (Fig. 1c). Estimation of the putative grid orientation
59 was achieved by fitting regressors for the sine and cosine of each saccade direction Φ in the respective
60 rotational symmetric space (e.g. 60° , 6-fold periodicity, along with biologically implausible 4-, 5-, 7- and 8-
61 fold control periodicities) to one half of the data (set 1) in a GLM. Saccade length was included as a
62 nuisance regressor in the analysis. The resulting phase-angle was extracted from the obtained beta
63 coefficients ($\Phi = \arctan(\beta_1/\beta_2)/\text{symmetry}$), in the respective rotational symmetric space. The other half
64 of the data (set 2) was binned according to Θ , into aligned bins ($\Phi \pm 15^\circ$, modulo 60°) and misaligned
65 bins ($\Phi + 30^\circ \pm 15^\circ$, modulo 60°). This procedure was repeated after swapping set 1 and set 2, and power
66 was averaged across the repetitions for aligned and misaligned bins, respectively.

67 We found significantly higher 60° periodic BHA (60-120 Hz) for aligned versus misaligned directional
68 sampling in the left anterior MTL, including entorhinal cortex ($t_{34} = 4.53$, $p < .00007$, Fig. 2a; Cohen's d
69 = .1988, reflecting a small effect size). When inspecting the 6 aligned and 6 misaligned 30° bins, aligned
70 directions generally elicited higher BHA power than misaligned directions (Fig. 2b), indicating that the
71 effect is not driven by a single direction. The putative grid orientations (i.e. the angle of the hexadirectional
72 modulation) did not cluster across participants (Fig. 2d). A 2x5 repeated-measures ANOVA with factors
73 alignment (aligned vs. misaligned) and rotational symmetry (4-, 5-, 6-, 7-, and 8-fold), revealed a significant
74 interaction ($F_{3,305, 112.3, \text{Greenhouse-Geisser}} = 3.49$, $p < .015$). Importantly, the significant quadratic contrast
75 (quadratic $F = 10.8$, $p < .0025$; linear and cubic contrasts not significant) indicated a u-inverted shape of
76 the differences across the rotational symmetries, being optimal for the 6-fold symmetry. Planned post-
77 hoc comparisons revealed that the difference for the 6-fold symmetry was bigger than for any of the other
78 symmetries (all t_{34} 's > 2.26 , all p 's $< .03$, 2-sided, uncorrected). Moreover, the differences for 4-, 5-, 7-,
79 and 8-fold symmetry were not significantly different from zero (all t_{34} 's < 1.2 & > -1.1 , all p 's $> .27$, 2-sided,
80 uncorrected, Fig. 2e). A repeated-measures ANOVA for the aligned bins in the MEG data showed no
81 significant difference ($F_{3,4,5} = 2.05$, $p = .075$). A repeated-measures ANOVA comparing the difference

82 (aligned – misaligned) across bins indicated that the effect was more pronounced for some directions
83 ($F_{34,5} = 2.28$, $p = .049$). No 6-fold modulation of BHA power was observed in right anterior MTL ($t_{34} = -.4$,
84 $p > .68$).

85 In addition, a whole-brain analysis of the 60° periodic modulation confirms the findings from the ROI-
86 based analysis and shows clustering of the highest differences between aligned and misaligned BHA
87 power in the left MTL (Fig. 2e), supporting the spatial specificity of the effect. To investigate whether the
88 hexadirectional modulation was limited to BHA, we computed the 60° periodic modulation of power in a
89 lower frequency band (20-50 Hz). There was no significant difference between aligned versus misaligned
90 directional sampling in the left anterior MTL ($t_{34} = 1.179$, $p = .247$). Furthermore, in the present analyses,
91 we investigated MEG activity during eye movements, which may be affected by oculomotor-related
92 artefacts. However, a 60° periodic BHA power modulation could not be found when oculomotor activity
93 recorded via EOG electrodes was analyzed ($t_{34} = 0.296$, $p > .769$; $t_{34} = -.9347$, $p > .357$; for horizontal and
94 vertical EOG signals, respectively; Fig. 2f). Moreover, there was no significant difference in number of
95 saccades aligned to the putative grid orientation versus number of saccades misaligned for 4-, 5-, 6-, 7-
96 and 8-fold rotational symmetries (see Fig. S2).

97 In order to investigate the possible electrophysiological origin and spatial specificity of the MEG results,
98 we analyzed intracranial data recorded from the entorhinal cortex of an epilepsy patient (Fig. S1a), while
99 the patient was performing a free viewing task. The BHA power difference (aligned – misaligned) was
100 significantly higher compared to a surrogate distribution in the 6-fold rotational symmetry ($p < .011$, 1-
101 sided; Fig. S1b&c). Biologically implausible 4-, 5-, 7-, and 8-fold symmetries did not show a significant
102 modulation of BHA power (all p 's $> .36$, one-sided; Fig. S1d), neither did a spatially adjacent amygdala
103 electrode (Fig. S1e) show a 6-fold rotational symmetry of BHA ($p > .36$; Fig. S1f&g). The difference between
104 the hexadirectional modulation of BHA in entorhinal cortex and amygdala was significantly higher than
105 expected by chance ($p < .013$).

106

107 **Discussion**

108 The present results provide the first evidence for a grid-like signal in non-invasive electrophysiological
109 recordings in humans: electromagnetic activity, source-localized to the anterior MTL, revealed a
110 hexadirectional modulation of BHA power (60 -120 Hz). Confirming these findings, intracranial field
111 potentials recorded in the entorhinal cortex of a patient also showed a hexadirectional modulation of BHA

112 power in the same frequency band. The whole-brain MEG as well as control analyses in the intracranial
113 data point towards the spatial specificity of the effect within the anterior MTL / entorhinal cortex. The
114 millisecond accuracy of these recordings allow to link activity to epochs during the relevant behavior,
115 thereby overcoming limitations of other non-invasive techniques, such as fMRI. We found a grid-like
116 pattern in BHA power, which has been suggested to correlate with local neural activity [12-15], indicating
117 that grid-coding is detectable with mass-electrophysiological recordings, opening up the possibility for
118 new non-invasive investigations of grid coding in cognitive neuroscience at high temporal resolution. We
119 show that the grid-like modulation of electromagnetic and intracranial electrophysiological activity is
120 related to the exploration of visual space. This is in line with work in non-human primates identifying cells
121 in the MTL that fire in relation to the animal's gaze position [8, 23-25], rather than coding location during
122 locomotion, as well as very recent fMRI work in humans showing hexadirectional modulations of
123 entorhinal BOLD activity related to the exploration of visual space [9, 10]. Given the fundamental
124 differences in sensory dominance between rodents and primates, it seems plausible that primates code
125 location during exploration by locomotion and eye movements.

126 In sum, our results support the view that grid-like coding in the anterior MTL goes beyond mapping the
127 environment during locomotion [8-10] and that the grid cell system could provide a general neural code
128 underlying core cognitive functions in humans [4-6, 11].

129

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144

145 **Author Contributions**

146 T.S., O.J. and C.F.D. designed the experiment. T.S., O.J and C.F.D wrote the paper. T.S. collected the data.
147 T.S. performed the analyses. M.L., C.E.S. designed, conducted the iEEG part of the study and assisted in
148 writing of the manuscript. S.A.S. implanted electrodes. J.J. provided electrode imaging information.

149 **Declaration of Interests**

150 The authors declare no competing interests.

151

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237

238 **Figure legends**

239 **Figure 1. Hexadirectional mapping of visual space: Procedure and Analysis.** (A) Paradigm: Free viewing
240 of 200 indoor / outdoor scenes with simultaneous eye tracking (left). MEG data are aligned to saccade
241 onsets, defining events of interest (middle). (B) Region-of-interest (highlighted), comprising bilateral
242 anterior portions of the hippocampus and parahippocampal gyrus. (C) Analysis rationale. Data was split
243 into halves (set 1, set 2) to estimate the putative grid orientation (angle of hexadirectional activity)
244 separately from computing aligned and misaligned BHA power, in a two-fold cross-validation design.
245 Estimation of putative grid orientation was done by fitting regressors for sine and cosine of saccade
246 directions (Θ) in the respective rotational symmetric space (here: 60° periodicity) to set 1 BHA power (the
247 general linear model included a constant and saccade duration as nuisance regressors). Resulting beta
248 estimates were used to derive the putative grid orientation angle (Φ). Trials in set 2 were split according
249 saccade directions aligned vs. misaligned to Φ . The difference in BHA power (aligned – misaligned) reflects
250 the grid-like modulation of BHA power.

251

252 **Figure 2. Grid-like modulation of BHA MEG activity during visual exploration.** (A) BHA power (60-120 Hz)
253 aligned to the putative grid orientation is significantly higher than misaligned BHA power in the left
254 anterior MTL. (B) 6-fold symmetric modulation of the BHA power, visualizing the effect in (A). The x-axis
255 depicts the difference between saccade directions and the estimated putative grid orientations. (C) Other
256 rotational symmetries (4-, 5-, 7- and 8-fold) do not show significant differences between aligned and
257 misaligned BHA power (D) Putative grid orientations across participants did not show clustering. (E)
258 Whole-brain analysis shows clustering of highest differences (aligned vs. misaligned, 60-120 Hz, 6-fold
259 symmetry) in the left temporal lobe. (F) No significant difference between aligned vs. misaligned BHA
260 power, in horizontal nor vertical EOG data (available in 32 participants). Dots show data from all
261 participants; Error bars show S.E.M. See also Figures S1 and S2.

262

263

264

265

266 **Star Methods**

267

268 **Contact for Reagent and Resource Sharing**

269 Further information and requests for resources and reagents should be directed to and will be fulfilled by
270 the Lead Contact, Tobias Staudigl (tobias.staudigl@cshs.org).

271 **Experimental Model and Subject Details**

272 36 young healthy adults were included in the MEG study. Initially, 48 participants were recruited;
273 however, 12 dropped out due to not completing the study (7 participants did not come back for one of
274 the sessions, see below), excessive movement artifacts (2 participants) and technical problems during the
275 recordings (3 participants). The 36 participants included in this study (24 females; mean age 23.1 years,
276 range 18-30 years; 35 right handed) reported no history of neurological and/or psychiatric disorders and
277 had normal or corrected-to-normal vision. One participant was excluded from the analysis due to
278 insufficient number of trials. Parts of this data have been published in Staudigl, et al. [30] with respect to
279 independent research questions and analyses. All participants gave written informed consent before the
280 start of experiment in accordance with the Declaration of Helsinki. The study was approved by the local
281 ethics committee (commission for human related research CMO-2014/288 region Arnhem/Nijmegen NL).
282 Additionally, one male patient (age range 25-45) with a history of drug resistant epilepsy was included in
283 the study. The patient, who volunteered to participate in the study at Columbia University Medical School,
284 had depth electrodes implanted for diagnostic reasons. All procedures were approved by the Institutional
285 Review Board at Columbia University Medical School. The patient provided informed consent before
286 participating in the study and was free to withdrawn from the study at any point. The study was approved
287 by the Institutional Review Board at Columbia University Medical School, New York City, US.

288

289 **Method Details**

290 **Design, Procedure and Materials.**

291 The design for the healthy participants comprised an MEG and an fMRI (not reported here) session. The
292 session order was counterbalanced across participants. Three stimulus sets, consisting of 100
293 photographs each, were constructed for each session. Half of the photographs were outdoor scenes, the
294 other half indoor scenes (see Fig. 1a, for an example). The photographs were presented on a 39 x 46 cm
295 back-projection screen in the MEG chamber, subtending a visual angle of approximately 27° × 32°. Two
296 stimulus sets were presented during encoding, all three sets during test. Assignment of set to encoding or

297 test was counterbalanced across participants. Nine additional scenes were presented during a short
298 practice session before encoding and test in order to explain the task. Participants were made aware
299 about the memory test before the start of the experiment. During the study phase, photographs were
300 presented for 4 s. The order was randomized with the constraint that no more than four scenes of the
301 same type (indoor / outdoor) were shown consecutively. The participants were instructed to judge the
302 scene type (indoor / outdoor) via a button press during the fixation cross (variable duration of 1 – 2 s)
303 following each scene (mean accuracy = .954, std = .068). This encoding task was chosen to ensure
304 attention to each scene. Participants were not expected to fixate, i.e. they freely viewed the scenes. The
305 study phase was followed by a distracter phase (solving simple mathematical problems for ~ 1 min), ~5
306 min of fixation to different locations on the screen used to evaluate eye tracker accuracy, and ~1 min of
307 eyes open and ~1 min of eyes closed. Subsequently, participants performed a recognition memory test
308 followed. Only data from the study phase are presented here.

309

310 **MEG Acquisition and Preprocessing.**

311 MEG was recorded in a magnetically shielded room, using a 275 whole-brain axial gradiometer system
312 (VSM MedTech/CTF MEG, Coquitlam, Canada). The data were sampled at a rate of 1200 Hz following a
313 low-pass anti-aliasing filter with a cutoff at 300 Hz. In addition, we recorded vertical and horizontal
314 electro-oculograms from bipolar Ag/AgCl electrodes (<10k Ω impedance; available for 32 participants)
315 placed below and above the left eye and at the bilateral outer canthi. 3 head coils placed at anatomical
316 landmarks (nasion and both ear canals) were used to track the position of the head relative to the MEG
317 helmet during the recordings. The head position was continuously monitored using a real-time head
318 localizer [31]. Each participant's nasion, left and right ear canal, and head shape were digitized with a
319 Polhemus 3Space Fasttrack. Data preprocessing was done using the Fieldtrip [27] toolbox. Data were
320 divided into single epochs, ranging from 0 to 4 s after scene onset, and corrected for cardiac artifacts using
321 Independent Component Analysis (ICA).

322

323 **Eye Tracking Acquisition, Analyses and Trial Definition.**

324 Eye tracking data were recorded simultaneously with MEG data. We tracked the horizontal and vertical
325 movements of each participant's left eye with an Eyelink 1000 (SR Research) eye tracker. The eye tracker
326 was calibrated before recording data, by collecting gaze fixation samples from known target points to map
327 raw eye data onto screen coordinates. Participants fixated nine dots sequentially appearing on a 3 by 3

328 grid. During the subsequent validation run, the difference between current gaze fixations and fixations
329 during the calibration were obtained. If this difference was smaller than 1 degree visual angle, the
330 calibration was accepted. Vertical and horizontal eye movements were transformed into velocities.
331 Velocities exceeding a given threshold (velocity > 6 x the standard deviation of the velocity distribution,
332 duration > 12 ms, see Engbert and Kliegl [32]) were defined as saccades. Saccade onsets during scene
333 presentation in the study phase defined the events of interest (trials). Only trials that were free of other
334 saccades and blinks in a 200 ms interval after saccade onset were included. On average, 558 (std = 196.9)
335 trials remained for the analysis. The trials were zero-padded to a length of 0.6 s (i.e., adding 200 ms of
336 zeros before and after the 200 ms of data). One participant was excluded from the analysis due to
337 insufficient number of trials for the hexadirectional analysis.

338 We focused our analysis on high frequency activity because it has been shown to correlate with local
339 neural activity [12-15] and was reported in the entorhinal cortex of behaving rodents [16]. We did not
340 analyze lower frequencies (e.g., theta) because our data epochs were too short to obtain a reasonable
341 frequency resolution in these bands.

342

343 **Source Reconstruction.**

344 Based on our a priori hypothesis on the origin of the grid signal in the entorhinal cortex, we performed a
345 region-of-interest based source reconstruction. To account for the spatial resolution of MEG, we
346 constructed two anterior medial temporal ROIs, comprising the anterior portions of the hippocampus and
347 parahippocampal gyrus in the left and right hemisphere, respectively (Figure 1b). For each hemisphere,
348 we aimed at computing one leadfield generated by the entire ROI, rather than averaging across multiple
349 point sources constructed within each ROI, applying a recently optimized MTL source reconstruction
350 method [17].

351 To construct the anterior medial temporal ROIs, we created 5 mm grids covering the voxels inside the
352 anterior half (median split) of anatomical masks including the labels 'Hippocampus_L',
353 'ParaHippocampal_L' and 'Hippocampus_R', 'ParaHippocampal_R', respectively, based on the Automatic
354 Anatomical Labeling atlas in Montreal Neurological Institute space [33].

355 For each participant, the MNI grid was warped onto each participant's anatomy bases on individual
356 structural MR images (1 mm isotropic voxels), acquired on a 3T Siemens Magnetom Prisma MRI system
357 (Siemens, Erlangen, Germany), after aligning the structural images to the MEG coordinate system, utilizing
358 the fiducials (nasion, left and right preauricular points) and individual head-shapes recorded after the

359 experiment. A realistic single-shell brain volume conduction model [34] was constructed for each
360 participant, based on these structural MRIs.

361 On the basis of this model, the contribution of dipolar sources at each grid point to the sensor level data
362 was estimated. Singular value decomposition was then used to reduce the columns of this sensor-by-grid
363 point leadfield matrix. The vector explaining most variance was selected, resulting in a leadfield matrix
364 consisting of one spatial component for each anterior medial temporal lobe ROI.

365 The cross-spectral density for the construction of the spatial filters was derived from the Fourier
366 transformation of all trials (epoch 0 to 200 ms from saccade onset) at the frequency of interest (90 Hz)
367 with 30 Hz spectral smoothing using a multitaper approach with 11 tapers from discrete prolate spheroidal
368 sequences (dpss). The cross-spectrum was regularized prior to matrix inversion by loading the diagonal of
369 the matrix with 5% of the average sensor power. We employed the Dynamic Imaging of Coherent Sources
370 (DICS) beamformer [35] to construct a spatial filter for each specified location. The sensor level single-trial
371 data was projected into source space by multiplying it with the spatial filter of each ROI, allowing for
372 further analysis to be conducted in virtual sensor space.

373 For the whole brain analysis (see Figure 2e), the same source estimation procedure was repeated for all
374 unique labels of the Automatic Anatomical Labeling atlas that include cortical brain areas.

375

376 **Hexadirectional analysis.**

377 The estimation of the hexadirectional signal followed a two-step procedure (see Fig. 1c): First, the putative
378 grid orientation was estimated on one half of the trials (a trial was defined by the onset of individual
379 saccades, see above). Second, aligned and misaligned (to the estimated putative grid orientation)
380 broadband high frequency activity (BHA) (60-120 Hz) power was computed. The procedure was repeated
381 with inversed assignment of data sets to the two steps, and aligned and misaligned BHA power was
382 averaged across the repetitions (two-fold cross-validation design).

383 Because of a horizontal bias in the distribution of saccade directions, we removed trials such that the
384 distribution of saccade directions in the analyses did not differ from a uniform distribution within
385 participants (Rayleigh-test, all p-values > .05). Performing a 4-,5-,6-,7- and 8-fold analyses of the saccades
386 directions yielded no significant difference between the number of saccades aligned and misaligned to
387 the putative grid orientation (4-fold: $t_{34} = -1.673$, $p=.104$; 5-fold: $t_{34} = -1.202$, $p=.238$; 6-fold: $t_{34} = -.392$,
388 $p=.698$; 7-fold: $t_{34} = -.82$, $p=.418$; 8-fold: $t_{34} = -.986$, $p=.3310$; see Fig. S2).

389 The remaining data was split into halves (set 1, set 2), and BHA power was computed for each set in virtual
390 sensor space by applying a sliding time window approach with a window length of 44 ms length in steps
391 of 10 ms across the data to each trial (epoched from saccade on- to offset, individual for each trial). After
392 multiplying a hanning taper to each window, the Fourier transformation was calculated at the frequency
393 of interest (90 Hz) with 30 Hz spectral smoothing using a multitaper approach with 2 dpss tapers. BHA
394 power was averaged across time bins within each trial, in cases where more than one BHA value resulted
395 from the sliding time window approach.

396 To estimate the putative grid orientation, regressors (β_1 , β_2) for sine and cosine of saccade directions (Θ)
397 in the respective rotational symmetric space (6-fold symmetry = 60° periodicity) were fitted to set 1 BHA
398 power using a general linear model including the saccade length (sl) as a nuisance regressor:

$$399 \quad y = \beta_0 + \beta_1 * \cos(6 * \theta) + \beta_2 * \sin(6 * \theta) + \beta_3 * sl + \varepsilon$$

400 Resulting beta estimates were used to derive the putative grid orientation (Φ):

$$401 \quad \Phi = \arctan(\beta_1 + \beta_2) / \text{symmetry}$$

402 The other half of the data (set 2) was binned according to each trial's saccade direction Θ , into aligned
403 bins ($\Phi \pm 15^\circ$, modulo 60°) and misaligned bins ($\Phi + 30^\circ \pm 15^\circ$, modulo 60°). BHA power was averaged
404 for aligned and misaligned bins, respectively.

405 After repeating the procedure with inversed assignment of data sets to the two steps, power was
406 averaged across the repetitions for aligned and misaligned bins, respectively. The difference in BHA power
407 (aligned – misaligned) reflects the grid-like modulation of BHA power. Biologically implausible 4-, 5, 7- and
408 8-fold periodicities were computed with the same approach and compared to the 6-fold periodic
409 modulation of BHA power.

410

411 **Intracranial data.**

412 One male patient (age range 25-45) with a history of drug resistant epilepsy was included in the study.
413 The patient was implanted with intracranial EEG electrodes for diagnostic purposes. Recordings were
414 performed at the Department of Neurological Surgery, Columbia University, USA. All procedures were
415 approved by the Institutional Review Board at Columbia University Medical School. The patient provided
416 informed consent before participating in the study and was free to withdrawn from the study at any point.

417 The procedure and design of the study was similar to the MEG procedure and design. The patient
418 performed a free viewing task with 80 coloured images (indoor and outdoor scene, faces, animals, etc.)
419 as stimuli. Each image was presented for 6 s in the center of a screen at a distance of about 65 cm,
420 subtending a visual angle of approx. $18^\circ \times 12^\circ$. The patient was requested to freely view each image. After
421 the stimulus offset a gray screen was displayed with five possible response options. The participant was
422 asked to indicate how he liked the last image on a scale ranging from 1 (very little) to 5 (very much) via
423 button press. The next image was displayed with a jitter interval of 0.1 to 0.5 s.

424 The locations of the electrodes were determined using pre- and post-operative MRIs and CTs, respectively
425 (for details see Jacobs, et al. [36]). One contact was identified to be fully located within the left entorhinal
426 cortex (indicated by red crosshair in Fig. S1A) and field potentials from this contact were used for further
427 analysis. To investigate spatial specificity of the hexadirectional modulation, a contact in the amygdala,
428 neighboring the entorhinal cortex (see Fig. S1E), was used to as a control site.

429 Intracranial EEG was recorded from depth electrodes (PMT Corporation) with multiple recording sites
430 (inter-contact spacing = 5 mm), using a Blackrock system (Blackrock Microsystems, Inc., Salt Lake City,
431 USA), with voltages referenced to an intracranial electrode site with least signal (2000 Hz sampling rate).
432 Data was re-referenced offline using a bipolar montage. Entorhinal data was re-referenced to the
433 contact's medial neighbor. Amygdala data was re-referenced to its lateral neighbor. A bipolar montage
434 provides high spatial specificity with respect to the underlying electric source and low susceptibility to
435 volume conducted artifacts (e.g. oculomotor artifacts).

436 Eye movements were monitored with a Tobii TX300 eye tracker. The left and right eye positions were
437 sampled at 300Hz. A five-point calibration was performed prior to experimental session. Intracranial EEG
438 data was offline downsampled to 1000 Hz and eye tracking data was interpolated to match sampling rate
439 at 1kHz. Subsequently, eye tracking and intracranial EEG data were co-registered and segmented into
440 epochs with 0.1 sec of prestimulus interval and 6 sec of stimulus presentation. All epochs were visually
441 inspected for artifacts (e.g. epileptiform spikes). Contaminated epochs were excluded from the analyses.
442 The eye tracking data was low-pass filtered at 30 Hz using a zero-phase forward and reverse butterworth
443 infinite impulse response filter.

444 Vertical and horizontal eye movements of the left eye were transformed into velocities. Velocities
445 exceeding a given threshold (velocity > 6 x the standard deviation of the velocity distribution, duration >
446 12 ms, see Engbert and Kliegl [32]) were defined as saccades. Saccade onsets during scene presentation

447 in the study phase defined the events of interest (trials). Only trials that were free of other saccades and
448 blinks in a 200 ms interval after saccade onset were included.

449 Intracranial EEG data were aligned to saccade onsets and BHA power was extracted during saccadic eye
450 movements. The trials were zero-padded to a length of 0.6 s (i.e., adding 200 ms of zeros before and after
451 the 200 ms of data). The estimation of the hexadirectional signal was identical to the procedure described
452 above (see Hexadirectional Analysis).

453

454 **QUANTIFICATION AND STATISTICAL ANALYSIS**

455 We tested the null-hypothesis that there is no difference between BHA power for aligned versus
456 misaligned saccade directions, in the left and right ROIs for the 6-fold rotational symmetry, using 2-sided
457 t-tests. To control for multiple comparisons, we adopted a significance level of 0.025. To measure effect
458 size Cohen's d was computed as

$$459 \quad d = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{s_1^2 + s_2^2 - 2rs_1s_2}/\sqrt{2(1-r)}}$$

460 with r denoting Pearson's correlation coefficient.

461 A 2x5 repeated-measures ANOVA with factors alignment (aligned vs. misaligned) and rotational symmetry
462 (4-, 5-, 6-, 7-, and 8-fold) was used to investigate the effect in the left anterior MTL. Planned post-hoc
463 comparisons (2-sided t-tests, uncorrected) were used to test the difference for the 6-fold symmetry versus
464 the other symmetries (4-, 5-, 7-, and 8-fold) and to test whether BHA power in the left anterior MTL were
465 different from zero for the biologically implausible 4-, 5-, 7-, and 8-fold rotational symmetries.

466 A further repeated-measures 1-way ANOVA with the factor rotational symmetry (4-, 5-, 6-, 7-, and 8-fold)
467 was used to test for differences among aligned bins in the MEG BHA. To investigate whether the
468 hexadirectional modulation was limited to BHA, a post-hoc t-test (2-sided, alpha level = .05) was
469 performed to test the 60° periodic modulation of power in a lower frequency band (20-50 Hz). As a further
470 post-hoc control analysis, two t-test (2-sided, alpha = .05, uncorrected) were used to test a 60° periodic
471 BHA power modulation recorded on EOG electrodes (for horizontal and vertical EOG signals, respectively).
472 Five post-hoc t-tests (2-sided, alpha = .05, uncorrected) were used to test the difference in number of
473 saccades aligned to the putative grid orientation versus number of saccades misaligned to the putative

474 grid orientation (for 4-, 5-, 6-, 7- and 8-fold rotational symmetries, respectively). All of the above analyses
475 were performed on the group level with N = 35.

476 We did not include a whole brain statistical approach (as for example implemented in the MEG/EEG
477 Fieldtrip Toolbox), because a significant outcome in this kind of test would only speak to the null
478 hypothesis (no difference between conditions) being rejected and not provide information on the exact
479 spatial extent of the effect [37].

480 The intracranial BHA power differences (aligned – misaligned) in one patient were statistically quantified
481 by comparing them to a distribution of surrogate BHA power differences. The surrogate distribution of
482 BHA power differences was constructed by randomly assigning trials to the aligned and misaligned
483 condition, respectively. 50000 surrogate BHA power differences were computed. Intracranial BHA power
484 differences were compared to the 50000 surrogate BHA power differences, and considered to be
485 significant if they were larger than the 95 % of the surrogate BHA power differences (one-sided test). This
486 procedure was used to quantify the 6-fold periodic modulation of BHA power, as well as the biologically
487 implausible 4-, 5-, 7- and 8-fold periodicities. Additionally, the difference between the hexadirectional
488 modulation of BHA in entorhinal cortex (aligned – misaligned) and amygdala (aligned – misaligned) was
489 compared to a distribution of 50000 surrogate BHA power differences. Differences were considered to be
490 significant if they were larger than the 95 % of the surrogate BHA power differences (one-sided test).

491

492

493 **Data and Software Availability**

494 Data and custom-built MATLAB scripts are available from the authors upon request.

495