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Early signal from the hippocampus for memory encoding

Running title: MTL and memory encoding

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Data available on request from the authors.

Abstract

The medio-temporal lobe (MTL), including the hippocampus, is involved in all stages of episodic memory including memory encoding, consolidation and retrieval. However, the exact timing of the hippocampus' involvement immediately after stimulus encounter remains unclear. In this study, we used high-density 156-channel electroencephalography (EEG) to study the processing of entirely new stimuli, which had to be encoded, in comparison to highly overlearned stimuli. Sixteen healthy subjects performed a continuous recognition task with meaningful pictures repeated up to four consecutive times. Waveform and topographic cluster analyses of event-related potentials revealed that new items, in comparison to repetitions, were processed significantly differently at 220-300 ms. Source estimation localized activation for processing new stimuli in the right MTL. Our study demonstrates the occurrence of a transient signal from the MTL in response to new information already at 200-300 ms post-stimulus onset, which presumably reflects encoding as an initial step towards memory consolidation.

Key words: encoding; medio-temporal lobe; hippocampus, novelty detection; EEG; event-related potentials

Introduction

The medio-temporal lobe (MTL), including the hippocampus, is involved in all stages of episodic memory (Scoville and Milner, 1957; Squire et al., 2004) including memory encoding (Davachi and Wagner, 2002; Paller and Wagner, 2002), consolidation (Nadel and Moscovitch, 1997; Dudai, 2004) and retrieval (Diana et al., 2007; Wixted and Squire, 2011; Rugg et al., 2012). Traditional models of memory encoding and consolidation (Cohen et al., 2015) suggest that memories are rapidly encoded in the hippocampus before becoming eventually independent of the hippocampus in later stages of memory consolidation (Frankland and Bontempi, 2005; Dudai et al., 2015; Squire et al., 2015).

While the role of the hippocampus minutes to hours after encoding appear to be well established (Dudai et al., 2015), the exact timing of the hippocampus' involvement in the first seconds after stimulus presentation remains unclear. Functional magnetic resonance imaging (fMRI) studies so far showed that novel faces (Ranganath and D'Esposito, 2001; Nichols et al., 2006) or natural scenes (Fuentemilla et al., 2010; Poch et al., 2011) maintained during a delay of 5-10 seconds elicited increased activity in MTL regions (Nichols et al., 2006) which in turn predicted later recognition (Ranganath et al., 2005). Other studies using fMRI demonstrated that immediate activity in the hippocampus at the offset of short audiovisual movie clips predicted subsequent memory, suggesting that this hippocampal signal is involved in encoding and could be an early step of memory consolidation (Ben-Yakov and Dudai, 2011; Dudai et al., 2015).

Recent studies using high-density electroencephalography (EEG), which has a much higher temporal resolution than fMRI, suggested that the MTL emits a transient encoding signal as early as 200-300 ms after stimulus presentation. Using a continuous recognition task, James et al. (2009) found that immediate repetition of pictures transiently activated the MTL in this period. Subsequent studies not only confirmed the hippocampal provenance of this signal using depth electrodes (Nahum et al., 2011), but also indicated a memory-protective effect (Thézé et al., 2016). Patients having amnesia due to Wernicke-Korsakoff disease (Nahum et al., 2015) or medial temporal stroke (Tautvydaitė et al., 2018) did not exhibit this signal. While these results unequivocally demonstrate early (200-300 ms) MTL involvement in the processing of immediate picture repetitions, the evidence for this signal to reflect encoding is only indirect.

The aim of the present study was to study early involvement of the MTL in memory encoding with a more direct paradigm. In particular, we wanted to verify that the MTL does indeed

emit an encoding signal as early as 200-300 ms after stimulus presentation. We thus designed a continuous recognition task composed of meaningful pictures. After first presentation, thought to induce encoding, pictures were immediately repeated up to four consecutive times, thus producing utmost familiarity, which presumably does not induce new encoding. To study encoding, we compared first presentations (requiring encoding) with overlearned repetitions.

Methods

Participants

Sixteen right-handed healthy individuals (eight women), aged 25±2 years (mean±SD), provided written, informed consent and were paid to participate in the study. They reported no history of neurological or psychiatric disorders or medication use. The Ethics Committee of the Canton of Geneva approved the study.

Procedure and task

Subjects performed three blocks of a continuous recognition task. Each block was composed of 60 color photographs representing objects, from the Bank of Standardized Stimuli (Brodeur et al., 2014). The 180 pictures were chosen for their familiarity (score > 3.5 on a 5-points scale) and visually analyzed to exclude pictures too similar in form or color. Each stimulus was presented for 1500 ms, followed by a 700 ms interval filled with a fixation cross. Participants were seated in a sound-attenuating booth in front of a 17-inch monitor positioned at eye-level. Stimulus delivery was controlled using E- prime 2.0. Each picture was presented once (New, n = 60) and subsequently repeated up to 3 or 4 times – hereafter referred to as the first repetition (R1, n = 120), second repetition (R2, n =120), third repetition (R3, n = 120) and fourth repetition (R4, n = 60). We focused our analyses on new presentations (New), immediate repetitions (R1) and fourth repetitions (R4). Participants were asked to indicate with respectively their right index or middle finger whether they had already seen the picture or not.

In addition, “catch” trials were inserted and included images without repetition (New catch, n = 60) and new pictures presented immediately following these catch trials (New-after-catch, n = 60). New catch and New-after-catch stimuli were only retained for control analyses and included to vary stimulus presentation and test for perceptual effects of stimulus change.

EEG acquisition and pre-processing

High-density electroencephalography (EEG) was continuously recorded during the task at 500 Hz using a 156-channel Brainvision system with actiChamp active electrodes (Brain Products GmbH, Germany). EEG data pre-processing and analyses were performed using the Cartool software (https://sites.google.com/site/cartoolcommunity/) developed by Brunet et al. (2011). Event-related potentials (ERPs) were calculated by averaging epochs from 100 ms before to 600 ms after the onset of the stimulus for each participant and each condition. Trials with incorrect answers or ±100mV artifacts were excluded, and the remaining epochs were inspected to remove those containing eye blinks or other transient noise. Channels showing recurrent artifacts for prolonged periods were interpolated from neighboring electrodes. Data were band-pass filtered (0.1–30 Hz), baseline corrected using the 100 ms pre-stimulus period and recalculated against the average reference. EEG accepted epochs were then averaged by condition. The average number (mean±SD) of accepted epochs was 36.38±7.9 for New, 35.13±7.74 for R1, 33.82±7.74 for R4, 35.13±5.49 for New catch and 37.19±5.61 for New-after-catch. Repeated measures one-way analysis of variance (rANOVA) with factor Stimulus (New, R1, R4, New catch and New-after-catch) revealed no statistical difference between the number of epochs accepted for each condition ($F_{(4,60)}$=1.252, p=0.299, η^2=0.077), ensuring that our results were not due to differences in signal-to-noise ratio between stimuli.

Statistical analysis of behavioral data

We analyzed behavioral data with one-way rANOVAs for both accuracy and reaction time (RT) with factor Stimulus (New, R1 and R4). We also ran a rANOVA with the three types of stimuli seen for the first time (New, New catch, New-after-catch) as a control condition. Post-hoc paired t-tests were Bonferroni corrected.

Waveform analysis

Time- and electrode-wise one-way rANOVA was performed on the ERP data for each of the 156 electrodes, with factor Stimulus (New, R1 and R4) as within subject factor. In order to decrease the risk of false-positives, only differences with a duration superior to 10 consecutive time points (i.e. 20 ms), significant at the threshold of p<0.01 and with a cluster criterion of at least eight neighboring electrodes (equivalent to 5% of the total of electrodes) were retained (Guthrie and Buchwald, 1991). The ERP waveform analysis was performed with the Statistical Toolbox for Electrical Neuroimaging (STEN) developed by Jean-

François Knebel (http://www.unil.ch/line/en/home/menuinst/about-the-line/software--analysis-tools.html). Although we analyzed a period up to 600ms, we focused mainly on the processes occurring before response execution. Response initiates in the motor cortex approximately 100ms before motor execution and the shortest RT occurred approximately at 470ms in our study, thus we considered only effects occurring before 400ms post-stimulus (Thorpe and Fabre-Thorpe, 2001). In order to control for perceptual/arousal effects, we also compared the waveform of New, New catch and New-after-catch, with a time- and electrode-wise one-way rANOVA, with the same criteria as for the stimuli of interest. Although items depicted in the pictures were highly familiar, we contrasted New presentation of highly familiar pictures (familiarity score in the Bank of Standardized Stimuli > 4.46) vs medium familiar pictures (score < 4.46) based on their original ratings, with a paired t-test using the same criteria as for the stimuli of interest.

Topographic cluster analysis

A topographic cluster analysis was performed on the ERPs to determine whether the configuration of brain's active generators changed between stimuli (Michel et al., 2004; Murray et al., 2008). This analysis is based on the assumption that the configuration

n of the electric field at the scalp surface remains stable for a certain time, before rapidly changing to another topography (Lehmann and Skrandies, 1980). Because a change in the topography of the electric field follows from a change in the configuration of the underlying intracranial generators, topographic changes are considered a direct interpretation of the engagement of different brain networks (Lehmann, 1987). Topographical cluster analysis therefore has the advantage of being reference-independent and unbiased by expectations about the timing or concerned electrodes in which differences might be observed (Tzovara et al., 2012).

Grand averaged ERPs for New, R1 and R4 were submitted to a topographic clustering analysis (Topographic Atomize and Agglomerate Hierarchical Clustering ; Brunet et al., 2011; Murray et al., 2008). The topographic analysis segments the time period in a limited number of ERP topographies (i.e. maps) based on a spatial cluster analysis. The optimal number of cluster maps is determined by cross-validation and the Krzanowski–Lai criterion. Their presence or absence, duration and temporal succession determines time periods during which different conditions elicit distinct electric fields (Pascual-Marqui et al., 1995; Michel et al., 2004, 2009). These time periods were then statistically tested by applying a spatial

correlation between grand averaged data and single subject ERPs. The result of this fitting procedure represents how long each map is present during the time window (in time frames, TF). These values were submitted to a two-way rANOVA with factor Stimulus (New, R1 and R4) and Map as within-subject factors, followed by simple effect tests for each map.

Source analysis

Finally, we estimated the origin of neural changes by submitting our data to a distributed linear inverse solution based on a Local Auto-Regressive Average (LAURA) (Grave De Peralta Menendez et al., 2004). The model used is composed of 4147 nodes distributed within the grey matter of the brain template provided by the Montreal Neurological Institute (MNI). LAURA tests which configuration of nodes better replicates the effective electrophysiological configurations. We extracted inverse solutions for the time period showing a significant main effect of Stimulus in the waveform analysis. The signal over this period of interest was averaged for each subject and source estimations were statistically compared at each solution point with a one-way rANOVA with the factor Stimulus (New, R1, R4) as within-subject factor. We retained only the effects significant at $p<0.01$ and with clusters of at least 15 nodes (see Knebel & Murray, 2012, for a similar procedure).

---------- Table 1 ----------

Results

Behavioral results

The task proved easy, as expected, with an overall high accuracy level (mean 97.31% ± 3.88) and fast response times (566.62 ms ± 138.50). Detailed results regarding all stimuli are showed in Table 1. Results of the ANOVA revealed a main effect of Stimulus for accuracy ($F_{(2,30)}=11.670$, $p<0.001$, $\eta_p^2=0.438$) and response time ($F_{(2,30)}=39.065$, $p<0.001$, $\eta_p^2= 0.723$). Post-hoc paired t-tests showed that R4 were faster ($p<0.001$) and better ($p<0.05$) recognized than New or R1.

---------- Figure 1 ----------

Waveform analysis

The electrode Fz is shown in Figure 1A as an exemplar waveform. Figure 1B shows the time- and electrode-wise ANOVA. This analysis revealed a statistically significant effect of Stimulus ($p<0.01$, >20 ms, >8 electrodes) at 220-300ms ($F_{(2,30)}>5.39$; $p<0.01$). Post-hoc analyses showed that New stimuli were processed differently than R1 and R4. The ANOVA also revealed a second time period between 440-600ms, where post-hoc tests indicated a different processing of New stimuli compared to both types of repetitions. Given the different reaction times, these late differences may reflect motor preparation.

The control analysis showed that waveforms in response to New catch and New after catch trials were similar to New in both periods (ANOVA, $F_{(2,30)}<5.39$; $p>0.01$). There were no differences either contrasting highly familiar pictures and medium familiar pictures (paired t-test, $t_{(15)}<2.60$; $p>0.01$).

Topographic cluster analysis

The topographic cluster analysis produced 8 different map configurations during the whole 600ms period (Fig. 1C). These maps identified at the group level explained 97.50% (Global Explained Variance, GEV) of the whole dataset. The first and most noteworthy difference appeared at 240-380ms post-stimulus onset, revealing a significant interaction between Stimulus and Map ($F_{(2,30)}=5.886$; $p=0.009$, $\eta_p^2=0.282$). The single-subject fitting procedure indicated a significantly different map configuration for processing of New stimuli ($p<0.01$) compared to R1 and R4 (Fig. 1D). This analysis confirmed the specific processing of New stimuli reported in the waveform analysis.

---------- Figure 2 ----------

Source analysis

Source analysis was performed on the averaged time period where significant differences appeared in the waveform analysis, that is from 220 to 300ms. Figure 2 shows that New stimuli, compared to R1 and R4, elicited significantly stronger activity ($p<0.01$, >15 nodes) in a right medio-temporal cluster comprising the hippocampus and parahippocampal gyrus, with extension into the lateral temporal lobe. Additional activation in a frontal cluster comprising the superior frontal gyrus and the anterior cingulate cortex was elicited for New compared to R1. By contrast, the difference between R1 and R4 was marginal and restricted to a frontal area in the paracentral lobule displaying stronger activity for R4.

Discussion

This study explored the timing of MTL mediated early encoding, as derived from the differential processing of entirely new, as opposed to highly overlearned stimuli in a continuous recognition task. High-resolution EEG revealed a transient signal emanating from the right MTL in response to New stimuli already at about 200-300 ms.

At the behavioral level, this task proved easy: repeated stimuli were better recognized than new presentations, which confirms the well-known behavioral priming effect, defined as a faster and more accurate processing of already experienced stimuli (Bentin and Moscovitch, 1988). Only first repetitions were less well recognized than following presentations, a result previously reported in a study using a similar continuous recognition paradigm with pictures repeated up to 3 times in a spaced manner (Yassa and Stark, 2008). As we included unrepeated stimuli (i.e. catch trials), the uncertainty when processing immediate repetitions may explain their weaker accuracy and slower response times compared to following repetitions.

Processing of new stimuli, in comparison to repeated stimuli, activated the right MTL at 220-300ms. This time window corresponds to the MTL signal reported in previous studies in response to immediate repetitions and which had been – indirectly – associated with memory encoding (James et al., 2009; Nahum et al., 2011; Thézé et al., 2016). By using a continuous recognition task in which familiar pictures are repeated in immediate succession up to 4 times, our task was effective in capturing the exact timing of this early MTL signal. We interpret this signal as a direct marker of memory encoding. This idea is compatible with the novelty/encoding hypothesis proposed by Tulving and Kroll (1995) which posits that novelty detection is an early stage of memory encoding (Tulving and Kroll, 1995; Ranganath and Rainer, 2003; Nyberg, 2005). Previous fMRI studies have indeed reported activation overlap in the MTL between novelty and encoding (Kim et al., 2010) or subsequent memory (Kirchhoff et al., 2000; Stark and Okado, 2003) or between novel and familiar items (Ranganath and Rainer, 2003; Kafkas and Montaldi, 2018). Furthermore, the magnitude of MTL signal at the offset of stimulus encoding has been shown to be modulated by stimulus novelty (Ben-Yakov et al., 2014). None of these studies provided a temporal resolution comparable to the present study.

The timing of MTL activation (220-300ms) is compatible with our interpretation of novelty signals guiding the early stages of memory encoding (Fernández and Tendolkar, 2006; Folstein et al., 2008). Novelty detection in oddball paradigms is typically reflected by N2 ERP

components peaking between 200-300ms (Czigler et al., 2006). Some authors have argued that novelty signals merely reflect increased perceptual and attentional bottom-up processes rather than memory encoding (Näätänen and Gaillard, 1983; Daffner et al., 1998; Ferrari et al., 2010). However, if novelty detection only reflected perceptual processes, we would not have found changes in a memory network. Further arguing against perceptual or arousal changes, our results did not show any difference between catch trials and presentation of new trials. There were no differences between highly familiar and medium familiar pictures, further arguing that novelty rather than familiarity is reflected by the transient EEG signal. To further disentangle novelty and familiarity (Habib et al., 2003), future studies should explore activity in response to unfamiliar pictures in similar paradigms.

Processing of new pictures activated the right MTL in this paradigm which appears congruent with fMRI studies reporting right MTL activity in response to pictorial novelty detection (Kirchhoff et al., 2000; Köhler et al., 2005; Yassa and Stark, 2008). This finding is however in contrast with previous studies showing activation of the left MTL during immediate repetitions (James et al., 2009; Nahum et al., 2011). However, these studies presented line drawings rather than photographs as in the present study. Futhermore, recent studies using the continuous recognition task showed that rather than being strictly confined to the left MTL, both MTLs appear to be involved during repetition of immediate pictures (Thézé et al., 2016; Tautvydaitė et al., 2018). Changes in experimental design, stimulus material or memory processes are factors known to influence lateralization of MTL activity (Schacter et al., 1995; Nyberg et al., 1996; Tulving et al., 1996; Kelley et al., 1998; Wagner et al., 1998; Manuel and Schnider, 2016).

In summary, this study provides first direct evidence for a transient encoding signal emanating from the MTL already at 200-300 ms after stimulus presentation.

References

Ben-Yakov A, Dudai Y. 2011. Constructing Realistic Engrams: Poststimulus Activity of Hippocampus and Dorsal Striatum Predicts Subsequent Episodic Memory. J Neurosci 31:9032–9042.

Ben-Yakov A, Rubinson M, Dudai Y. 2014. Shifting Gears in Hippocampus: Temporal Dissociation between Familiarity and Novelty Signatures in a Single Event. J Neurosci 34:12973–12981.

Bentin S, Moscovitch M. 1988. The time course of repetition effects for words and unfamiliar faces. J Exp Psychol Gen 117:148–160.

Brodeur MB, Guérard K, Bouras M. 2014. Bank of Standardized Stimuli (BOSS) phase ii: 930 new normative photos. PLoS One 9.

Brunet D, Murray MM, Michel CM. 2011. Spatiotemporal analysis of multichannel EEG: CARTOOL. Comput Intell Neurosci 2011.

Cohen N, Pell L, Edelson MG, Ben-Yakov A, Pine A, Dudai Y. 2015. Peri-encoding predictors of memory encoding and consolidation. Neurosci Biobehav Rev 50:128–142.

Czigler I, Winkler I, Pató L, Várnagy A, Weisz J, Balázs L. 2006. Visual temporal window of integration as revealed by the visual mismatch negativity event-related potential to stimulus omissions. Brain Res 1104:129–140.

Daffner KR, Mesulam MM, Scinto LFM, Cohen LG, Kennedy BP, West WC, Holcomb PJ. 1998. Regulation of attention to novel stimuli by frontal lobes: An event- related potential study. Neuroreport 9:787–791.

Davachi L, Wagner AD. 2002. Hippocampal Contributions to Episodic Encoding: Insights From Relational and Item-Based Learning. J Neurophysiol 88:982–990.

Diana RA, Yonelinas AP, Ranganath C. 2007. Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cogn Sci 11:379–386.

Dudai Y. 2004. The Neurobiology of Consolidations, Or, How Stable is the Engram? Annu Rev Psychol 55:51–86.

Dudai Y, Karni A, Born J. 2015. The Consolidation and Transformation of Memory. Neuron 88:20–32.

Fernández G, Tendolkar I. 2006. The rhinal cortex: ‘gatekeeper’ of the declarative memory system. Trends Cogn Sci 10:358–362.

Ferrari V, Bradley MM, Codispoti M, Lang PJ. 2010. Detecting novelty and significance. J

Cogn Neurosci 22:404–11.

Folstein JR, Van Petten C, Rose SA. 2008. Novelty and conflict in the categorization of complex stimuli. Psychophysiology 45:467–479.

Frankland PW, Bontempi B. 2005. The organization of recent and remote memories. Nat Rev Neurosci 6:119–30.

Fuentemilla L, Penny WD, Cashdollar N, Bunzeck N, Düzel E. 2010. Theta-Coupled Periodic Replay in Working Memory. Curr Biol 20:606–612.

Grave De Peralta Menendez R, Murray MM, Michel CM, Martuzzi R, Gonzalez Andino SL. 2004. Electrical neuroimaging based on biophysical constraints. Neuroimage 21:527–539.

Guthrie D, Buchwald JS. 1991. Significance testing of difference potentials. Psychophysiology 28:240–244.

Habib R, McIntosh AR, Wheeler MA, Tulving E. 2003. Memory encoding and hippocampally-based novelty/familiarity discrimination networks. Neuropsychologia 41:271-279

James C, Morand S, Bareellona-Lehmann S, Michel CM, Schnider A. 2009. Neural transition from short-term to long-term memory and the medial temporal lobe: A human evoked-potential study. Hippocampus 19:371–378.

Kafkas A, Montaldi D. 2018. How do memory systems detect and respond to novelty? Neurosci Lett.

Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, Ollinger JM, Akbudak E, Conturo TE, Snyder AZ, Petersen SE. 1998. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron 20:927–36.

Kim H, Daselaar SM, Cabeza R. 2010. Overlapping brain activity between episodic memory encoding and retrieval: Roles of the task-positive and task-negative networks. Neuroimage 49:1045–1054.

Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000. Prefrontal-Temporal Circuitry for Episodic Encoding and Subsequent Memory. J Neurosci 20:6173–6180.

Knebel J, Murray MM. 2012. Towards a resolution of conflicting models of illusory contour processing in humans. Neuroimage 59:2808–2817.

Köhler S, Danckert S, Gati JS, Menon RS. 2005. Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: A

comparison based on event-related fMRI. Hippocampus 15:763–774.

Lehmann D. 1987. Principles of spatial analysis. In: Handbook of electroencephalography and clinical neurophysiology, vol 1. Methods of analysis of brain electrical and magnetic signals. Vol. 1. Elsevier. p 309–354.

Lehmann D, Skrandies W. 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr Clin Neurophysiol 48:609–621.

Manuel AL, Schnider A. 2016. Differential processing of immediately repeated verbal and non-verbal stimuli: An evoked-potential study. Eur J Neurosci 43:89–97.

Michel CM, Koenig T, Brandeis D, Gianotti LRR, Wackermann J. 2009. Electrical Neuroimaging. Cambridge, NY: Cambridge University Press.

Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave De Peralta R. 2004. EEG source imaging. Clin Neurophysiol 115:2195–2222.

Murray MM, Brunet D, Michel CM. 2008. Topographic ERP analyses: A step-by-step tutorial review. Brain Topogr 20:249–264.

Näätänen R, Gaillard AWK. 1983. The Orienting Reflex and the N2 Deflection of the Event-Related Potential (ERP). Adv Psychol 10:119–141.

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7:217–227.

Nahum L, Gabriel D, Spinelli L, Momjian S, Seeck M, Michel CM, Schnider A. 2011. Rapid consolidation and the human hippocampus: Intracranial recordings confirm surface EEG. Hippocampus 21:689–693.

Nahum L, Pignat J-M, Bouzerda-Wahlen A, Gabriel D, Liverani MC, Lazeyras F, Ptak R, Richiardi J, Haller S, Thorens G, Zullino DF, Guggisberg AG, Schnider A. 2015. Neural Correlate of Anterograde Amnesia in Wernicke–Korsakoff Syndrome. Brain Topogr 28:760–770.

Nichols EA, Kao Y-C, Verfaellie M, Gabrieli JDE. 2006. Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. Hippocampus 16:604–16.

Nyberg L. 2005. Any novelty in hippocampal formation and memory? Curr Opin Neurol 18:424–428.

Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E. 1996. Activation of medial temporal structures during episodic memory retrieval. Nature 380:715–717.

Paller KA, Wagner AD. 2002. Observing the transformation of experience into memory. Trends Cogn Sci 6:93–102.

Pascual-Marqui RD, Michel CM, Lehmann D. 1995. Segmentation of brain electrical activity into microstates: model estimation and validation. Biomed Eng IEEE Trans 42:658–665.

Poch C, Fuentemilla L, Barnes GR, Düzel E. 2011. Hippocampal theta-phase modulation of replay correlates with configural-relational short-term memory performance. J Neurosci 31:7038–42.

Ranganath C, Cohen MX, Brozinsky CJ. 2005. Working Memory Maintenance Contributes to Long-term Memory Formation: Neural and Behavioral Evidence. J Cogn Neurosci 17:994–1010.

Ranganath C, D'Esposito M. 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31:865–873.

Ranganath C, Rainer G. 2003. Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4:193–202.

Rugg MD, Vilberg KL, Mattson JT, Yu SS, Johnson JD, Suzuki M. 2012. Item memory, context memory and the hippocampus: FMRI evidence. Neuropsychologia 50:3070–3079.

Schacter DL, Reiman E, Uecker A, Roister MR, Yun LS, Cooper LA. 1995. Brain regions associated with retrieval of structurally coherent visual information. Nature 376:587–590.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neuropsychiatry Clin Neurosci 20:11–21.

Squire LR, Genzel L, Wixted JT, Morris RGM, Wisted JT, Morris RGM. 2015. Memory Consolidation. Cold Spring Harb Perspect Biol 7:a021766.

Squire LR, Stark CEL, Clark RE. 2004. the Medial Temporal Lobe*. Annu Rev Neurosci 27:279–306.

Stark CEL, Okado Y. 2003. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. J Neurosci 23:6748–53.

Tautvydaitė D, Manuel AL, Nahum L, Adam-Darqué A, Ptak R, Schnider A. 2018. Absence of an early hippocampal encoding signal after medial temporal lesions: no consequence for the spacing effect. Hippocampus

Thézé R, Guggisberg AG, Nahum L, Schnider A. 2016. Rapid memory stabilization by

transient theta coherence in the human medial temporal lobe. Hippocampus 26:445–454.

Thorpe SJ, Fabre-Thorpe M. 2001. Neuroscience. Seeking categories in the brain. Science 291:260–263.

Tulving E, Kroll N. 1995. Novelty assessment in the brain and long-term memory encoding. Psychon Bull Rev 2:387–390.

Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S. 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 6:71–9.

Tzovara A, Murray MM, Michel CM, De Lucia M. 2012. A Tutorial Review of Electrical Neuroimaging From Group-Average to Single-Trial Event-Related Potentials. Dev Neuropsychol 37:518–544.

Wagner AD, Poldrack RA, Eldridge LL, Desmond JE, Glover GH, Gabrieli JDE. 1998. Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. Neuroreport 9:3711–3717.

Wixted JT, Squire LR. 2011. The medial temporal lobe and the attributes of memory. Trends Cogn Sci 15:210–7.

Yassa MA, Stark CEL. 2008. Multiple signals of recognition memory in the medial temporal lobe. Hippocampus 18:945–954.

Tables and Figures

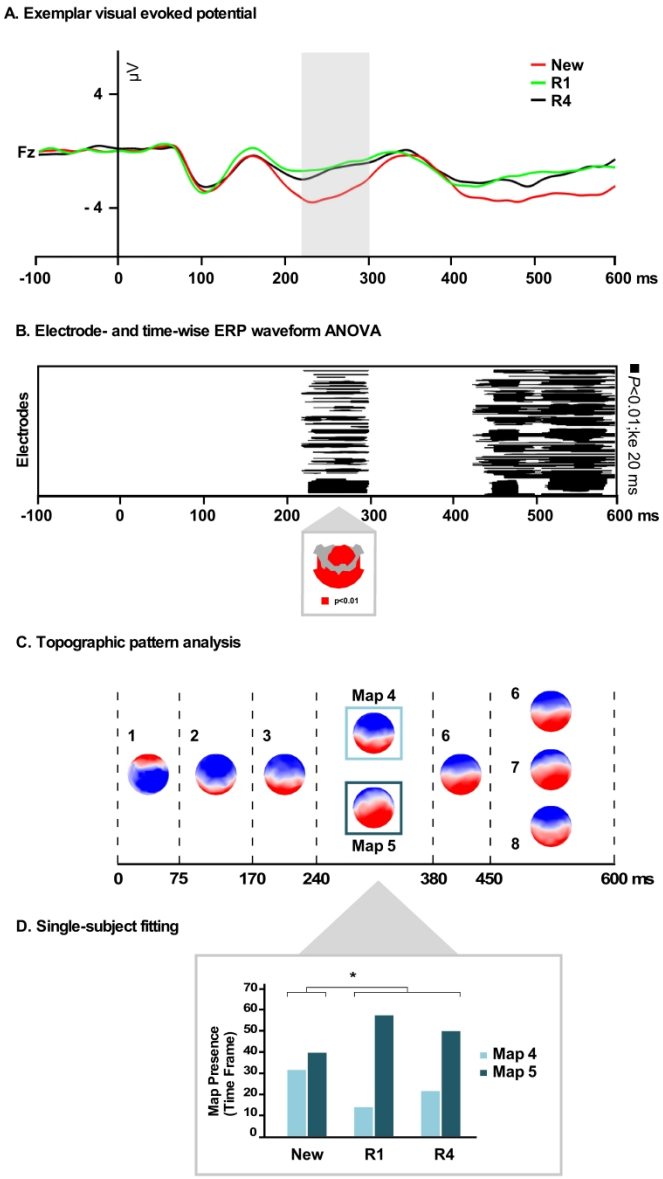
Table 1

	Accuracy (% correct)	Response time (ms)
New	97.5 ± 3.22	617.82 ± 110.04 *
R1	93.93 ± 5.50 *	603.73 ± 94.99 *
R2	98.18 ± 2.79	469.06 ± 85.65
R3	99.06 ± 1.85	449.65 ± 79.19
R4	99.48 ± 1.32	471.7 ± 86.53

Table 1. Behavioural results (mean±SD) for the continuous recognition task. * indicates a significant difference at the $p<0.01$ level in post-hoc paired t-test tests following the one-way ANOVA on the three stimuli of interest.

Fig. 1. EEG results. **A**. Grand average ERP waveforms from the exemplar frontal electrode Fz in response to New (red), R1 (green) and R4 (black). The area in grey depicts the period of significant amplitude differences between conditions revealed by the waveform analysis. **B**. Results of the electrode- and time-wise ERP waveform analysis. The one-way repeated-measure ANOVA showed a significant main effect of Stimulus (New, R1 and R4) at 220-300ms as indicated by black lines ($p<0.01$, >20ms, 8 electrodes). Electrodes with significant differences are displayed on red on the scalp map. **C**. Topographic cluster analysis yielded 8 distinctive scalp maps during the 600ms post-stimulus period. Between 240-380ms two maps were present. **D**. Results of the single-subject fitting showing the map presence (in time frames) for each map and Stimulus during the 240-380ms time period. The 3 (Stimulus) x 2 (Map) ANOVA results confirmed that the significant interaction was driven by a stronger presence of map 4 in responses to New trials.

Fig. 2. Source estimations. Results of neural source estimation analysis on the averaged time period showing significant differences between conditions (220-300ms). The figure displays the results of the post-hoc paired t-test comparing New, R1 (first repetition) and R4 (fourth repetition). Color meanings are indicated in the scale.



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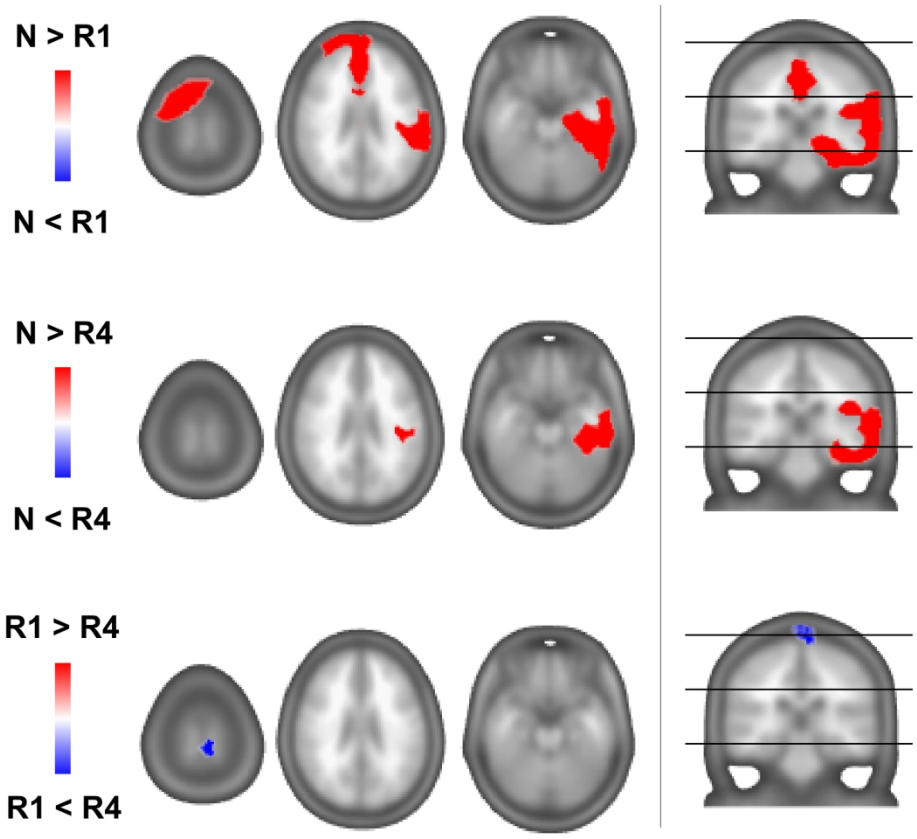
359x631mm (300 x 300 DPI)



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155x139mm (300 x 300 DPI)