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ORIGINAL ARTICLE

Distinct Neurophysiological Mechanisms Support the Online Formation of Individual and Across-Episode Memory Representations

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Abstract

Individual experiences often overlap in their content, presenting opportunities for rapid generalization across them. In this study, we show in 2 independent experiments that integrative encoding—the ability to form individual and across memory representations during online encoding—is supported by 2 distinct neurophysiological responses. Brain potential is increased gradually during encoding and fit to a trial level memory measure for individual episodes, whereas neural oscillations in the theta range (4–6 Hz) emerge later during learning and predict participants' generalization performance in a subsequent test. These results suggest that integrative encoding requires the recruitment of 2 separate neural mechanisms that, despite their co-occurrence in time, differ in their underlying neural dynamics, reflect different brain learning rates and are supportive of the formation of opposed memory representations, individual versus across-event episodes.

Key words: EEG, ERP, generalization, inferential learning, theta rhythm

Introduction

Memories do not simply consist of individual records of directly experienced events, but also include representations built by relating information acquired across multiple discrete episodes (Eichenbaum 1999). Flexibility in combining memories in novel ways to infer new information is essential to behavior in an ever-changing environment, and the study of the underlying neural mechanisms has become a great challenge in cognitive-, theoretical-, and systems-level memory research (Kumaran and McClelland 2012; Zeithamova et al. 2012a; Preston and Eichenbaum 2013).

A simple, effective way to organize both the specific and the relational information accrued across memories is to encode common features of related experiences into the same representational elements (Cohen and Eichenbaum 1993; Eichenbaum 1999; O'Reilly and Rudy 2001). Thus, encountering an event that has features overlapping with previously encoded events can trigger retrieval of memory of the past events, and this, in turn, can lead to the encoding of discrete events in an integrated representation. This mechanism has been termed "integrative encoding" and it allows direct storage in memory of the relation between elements that were not experienced together (Shohamy and Wagner 2008). Thus, on testing, generalization is not a

reconstructive inference-based process based on flexible retrieval of multiple memories (Dusek and Eichenbaum 1997; Heckers et al. 2004; Preston et al. 2004; Greene et al. 2006) but rather is a direct expression of knowledge encoded in memory as a synthesis of information across multiple experiences. The fundamental advantage of integrative encoding is, therefore, that it allows the detection and the encoding of generalizations as events unfold over time and the storing of these generalizations as memories, making them available when needed in the future.

Central to integrative encoding is the assumption that the retrieval of previous event episodes and the formation of an integrated representation that binds together information across episodes are rapidly intertwined during encoding and that they rely on different neural mechanisms coordinated by the hippocampus (O'Reilly and Rudy 2001; Shohamy and Wagner 2008; Zeithamova and Preston 2010; Kumaran and McClelland 2012; Zeithamova et al. 2012a). While one neural response would signal the process of retrieval of individual memories, another neural response would index the recruitment of memory processes, supporting inferential learning or generalization. Thus, theoretical work (McClelland et al. 1995) has long established that the encoding of specific events from the past (e.g., A follows B and B follows C) and the formation of a general structure of our experiences (A follows C) requires the engagement of 2 different neural coding mechanisms (Kumaran and McClelland 2012), both targeting the involvement of the hippocampus as well as the hippocampus–neocortical interaction (McClelland et al. 1995; Norman and O'Reilly 2003). In doing so, the brain can deal with the computational tension of encoding and retrieving individual episodes while being able to extract the commonalities based on overlapping elements with other existing memory episodes (Norman and O'Reilly 2003). These 2 neural mechanisms should be operatively identifiable on the basis of testable predictions. First, because generalization depends on having learned the individual episodes, memory integration should occur later, rather than earlier, in learning. Thus, the neural mechanisms supporting the retrieval of individual event memories and across-episode (i.e., inferred) memory representations should appear distinctly over the course of learning a task. And second, given that the succession of event episodes in real life is very fast, these 2 processes should take place very rapidly, possibly during online encoding.

In this study, we sought to test the hypothesis that distinct neurophysiological mechanisms support the online formation of individual and across-episode memory representations, thought to underlie integrative encoding. To address this question, we recorded scalp electrophysiological (EEG) signals in 2 independent experiments from 70 participants while they were engaged in an adapted version of associative learning and generalization tasks (Shohamy and Wagner 2008). The fine-grained temporal resolution of the EEG allows us to investigate the neural dynamics sustained during very rapid cognitive operations, which is critical to test the prediction that neural mechanisms should appear intertwined and occur very rapidly during encoding. In addition, different neural mechanisms can be simultaneously measured with EEG activity, thereby enabling the possibility that 2 neural signals to be measured independently of each other. Concretely, we investigated the possibility that integrative encoding is supported by evoked neural responses, registered as event-related potentials (ERPs) and changes in ongoing neural oscillatory activity, specifically in the theta range (3–9 Hz). Indeed, the combined study of ERPs and neural oscillations has provided critical insights into the timing and the neural dynamics operating during encoding, maintenance and memory retrieval episodes (Düzel et al. 1997; Rugg et al. 1998; Paller and Wagner 2002; Düzel et al. 2010), and they have been shown to be sensitive to medial temporal lobe lesions (including the hippocampus) (Düzel et al. 2001).

First, successful recollection of a memory episode upon cue presentation triggers a slow ERP component rising after ~500 ms at posterior scalp regions, known as late posterior component (LPC) (Curran 2000; Friedman and Johnson 2000). LPC has been shown to arise during the successful retrieval of episodic but not semantic memory information and to be hippocampus-dependent (Düzel et al. 2001; Horner et al. 2012), thereby being well established nowadays as an EEG signature of explicit retrieval of an event episode. Because integrative encoding requires the reinstatement of previous event memories from partial cues, we predict that LPC signals the ability to remember episodic events and that LPC modulation occurs at the expense of the ability to generalize novel events.

Furthermore, the possibility that neural oscillations in the theta range are critical in integrative encoding is motivated by theoretical models and neurophysiological data from animals that suggest that the hippocampus dynamically shifts between encoding and retrieval states (Hasselmo et al. 1995; Hasselmo and McClelland 1999), thus serving as a regulatory mechanism of encoding/retrieval-derived communication with neocortical regions (Hasselmo and Eichenbaum 2005). In fact, the hippocampus–neocortex network is a primary conduit for cerebral information flow between learning and memory. It has been proposed that the hippocampus creates "pointer" representations, linking together activity in multiple cortical areas pertaining to the representation of information from different overlapping episodes and facilitating the formation of a joint representation integrating multiple interrelated event episodes (O'Reilly and Norman 2002). Importantly, effective communication between the hippocampus and the neocortex involves oscillations. For instance, the prefrontal cortex, which receives monosynaptic hippocampal projections (Jay and Witter 1991; Thierry et al. 2000), has been shown to be functionally connected to the hippocampus: hippocampal theta synchronizes prefrontal cortex neurons (Siapas et al. 2005) and local field potentials (Hyman et al. 2005), and the degree of hippocampus-prefrontal theta synchrony increases during the course of successful encoding in a task (Benchenane et al. 2010). Furthermore, animal (Jones et al. 2012) and functional (Wimmer and Shohamy 2012; Zeithamova et al. 2012b) as well as structural (Gerraty et al. 2014) neuroimaging studies in humans have shown that the hippocampus–neocortical network may be critical to the formation and use of flexible representations to guide choices and actions in the future. Thus, in the current investigation we reasoned that theta oscillations would be critically associated with the formation of integrative memories during encoding, thereby supporting generalization performance in a later test.

In the current investigation, we adapted an acquired equivalence task developed by Shohamy and Wagner (2008) (Fig. 1A; Task Design). The task was structured in 2 encoding phases, each of them followed by a test phase (Fig. 1A). On each trial of the encoding phase, participants learned to associate a face with a scene via a recognition memory test in which they were requested to choose which of 2 scenes went with the face, and then received feedback. While each face-scene association was encoded individually, there was partial overlap across events, so that pairs of faces were associated with a common scene (e.g., F1–S1; F2–S1). In addition to learning the F1–S1 and F2–S1 associations, participants were concurrently trained in a

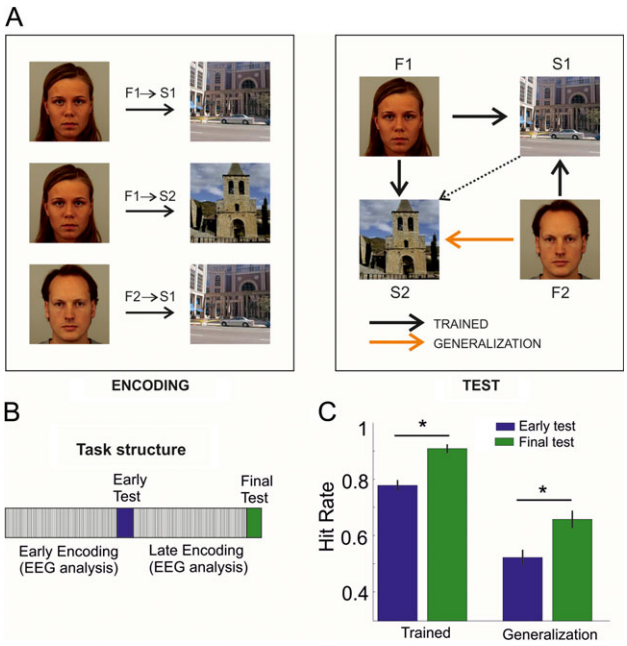

Figure 1. Schema of the experimental design and behavioral results. (*A*) Overview of the acquired equivalence task (Shohamy and Wagner 2008) and (*B*) schema of how early and late encoding trials were distributed throughout the task. (*C*) Histogram of participants' performance for trained and inference trials at the late test. Note that participants correctly learned individual associations, but there was great variability in their ability to generalize them to novel pairs.

second association for one of the faces (i.e., F1–S2; Fig. 1A). Thus, the initial encoding phase consisted of 3 different types of stimulus combinations that contained partial overlap (F1–S1; F2–S1; F1–S2). Therefore, while it is expected that the overlap between F1–S1 and F2–S1 elicited across-episode integration during learning, the additional learning of the F1–S2 association would lead F2 to also become associated with S2 (Grice and Davis 1960; Hall et al. 1993; Collie et al. 2002).

Following each of the 2 encoding phases, a test phase tested participants' ability to generalize. Specifically, generalization trials tested whether participants would choose S2 when presented F2 even though they had never encountered this pairing at study (Fig. 1A). These generalization trials were tested together with trials that examined retention of knowledge about the associations that had been previously encountered (F2–S1; F1–S1; F1–S2; "trained"). Feedback was not provided during this phase, to prevent new learning occurring across test trials.

Materials and Methods

Participants and Material

A total of 70 right-handed volunteers (28 males) participated in the 2 experiments ($N = 37$ in Experiment 1; $N = 33$ in Experiment 2). Mean age for participants was 23.5 years (SD = 5.4 years). All participants had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the University of Barcelona and all participants gave written consent before starting the experiment. All participants received 20€ for participation. In all, 37 participants participated in Experiment 1 and 33 participated in Experiment 2.

The stimuli consisted of 24 faces taken from a standardized database (Lundqvist et al. 1998) and 24 scenes (12 natural landscapes and 12 urban scenes). Stimuli were structured into 12 subsets, such that 2 faces (F1, F2) were paired with 2 scenes (S1, S2), so that we could obtain 4 associations for every subset: F1–S1, F1–S2, F2–S1, and F2–S2. As for the second experiment, 88 faces and 152 scenes from different databases (Minear and Park 2004; Langner et al. 2010; Xiao et al. 2010) were used. Twenty-four faces and 24 scenes were used for the 12 subsets of associations and the remaining 64 faces and 128 scenes served as novel stimuli (fillers) and were presented throughout the task.

Task Design

Experiment 1

The paradigm was adapted from the learning and generalization task described by Shohamy and Wagner (2008). The task consisted of 3 phases: preexposure, encoding, and test. We included the preexposure phase to avoid/reduce variability in the structure of the task although the study led by Shohamy and Wagner (2008) demonstrated that preexposure to the stimuli has no effect on the tasks. Therefore, we did not analyze the corresponding data. Following preexposure, there was the encoding phase, during which participants learned a series of face-scene associations using feedback. The generalization process was expected to occur during this phase. After this, in order to measure participants' retention and their capacity to generalize, participants were tested on the previously learned associations and on new face-scene combinations meant to be solved by generalization. In the test phase, no feedback was provided. Both the encoding and test phases were performed twice in a row so that there was a first encoding and test followed by a second encoding plus test.

During the preexposure phase, half of the stimuli that would appear throughout the task were displayed individually. Participants were asked to indicate with the right and left arrows of the keyboard whether the stimulus they were seeing was a person or a scene. Trials consisted of the appearance of a single stimulus (Face or Scene) presented in the center of the screen for 1250 ms. Presentation of male/female and landscape/urban scene categories was counterbalanced by presenting each stimulus 8 times. In order to randomize and distribute the 8 repetitions throughout the preexposure phase, we divided the 24 stimuli (12 faces, 12 scenes) into 4 blocks of 48 trials from which each stimulus was presented twice. The order of presentation of each block was randomized across participants.

Regarding the encoding phase, 3 associations of each of the previously formed subsets were trained (F1–S1, F1–S2, and F2–S1). Each trial consisted of the presentation of a face at the top of the screen and 2 scenes at the bottom for 2500 ms. Participants had to wait for the appearance of the message "RESPONSE" and they then had 1000 ms to indicate by pressing a button which of the 2 scenes was associated with the face. Following participants' choices, a delay period (gray background) of 1000 ms preceded the feedback, which consisted of the presentation of either a pictograph of a smiling face (right choice) or a pictograph of a sad face (wrong choice), and it remained on the center of the screen for 1000 ms. At each stage (first encoding and second encoding), each association was shown 4 times in random order, so that by the end of the task, each pair was presented 8 times. The appearance of the scenes on the right or left side of the screen was counterbalanced through the 8 presentations. Additionally, in order to avoid stimulus–response learning strategies, every scene was shown as a correct choice for a particular face and also as an incorrect choice when appearing with other faces, with the restriction

that it could not appear twice as an incorrect choice with the same face. Therefore, the correct scene for a given face was always the same, but the incorrect scene was variable.

During the test phase all the possible associations of each subset, the trained ones (F1–S1, F2–S1, and F1–S2) and the untrained ones (F2–S2), were presented in random order. The structure of the presentation was the same as in the encoding phase (1 face, 2 scenes), but in this case, pictures remained on screen until the participants responded, and there was no feedback informing the participants of the result of their choice. In both the first and the second test, each association was presented a single time and the side of the scene was counterbalanced between the 2 tests. In all three phases, trials were separated by an inter-trial time randomized between 750 and 1250 ms.

Experiment 2

The task design in Experiment 2 was the same as in Experiment 1, except that throughout the entire task, there were 64 presentations composed of faces and scenes that would only appear once (fillers) during encoding and never presented in the test. Also participants were not preexposed to all items before encoding. Fillers were distributed randomly during encoding but homogeneously distributed throughout the task so that there was 8 fillers for each of the 8 repetitions of the encoding. Feedback for these novel stimuli was random so that 50% of the responses would be given as correct and 50% as incorrect.

EEG Recording

In the 2 experiments, EEG was recorded (band-pass filter: 0.01–250 Hz, notch filter at 50 Hz, and 500 Hz sampling rate) from the scalp using a BrainAmp amplifier and tin electrodes mounted in an electrocap (Electro-Cap International) located at 29 standard positions (Fp1/2, Fz, F7/8, F3/4, FCz, FC1/2, FC5/6, Cz, C3/4, T3/4, Cp1/2, Cp5/6, Pz, P3/4, T5/6, PO1/2, Oz) and at the left and right mastoids. An electrode placed at the lateral outer canthus of the right eye served as an online reference. EEG was re-referenced offline to the linked mastoids. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the right eye. Electrode impedances were kept below 5 kΩ. EEG was low-pass filtered offline at <16 Hz for ERP analysis.

ERP Analysis

For each participant, EEG data were studied from cue trials of the first and second encoding phases. ERPs were studied by extracting response-locked EEG epochs of 2000 ms starting at 100 ms before the cue onset. This time period corresponds to the interval in which cue-associations are presented and allegedly learned. Consequently, this was the time window in which we expected to discern a distinctive effect of memory recollection such as a modulation of the late positive component (LPC, Friedman and Johnson 2000). Trials exceeding ± 100 μV in both EEG and EOG within 0–2000 ms time window were rejected offline and not used in the ERP and in the time-frequency (TF) analysis detailed below. The average number of trials included in the analysis in Experiment 1 was 111.78 (range: 34–142) for Early encoding and 107.18 (range: 29–137) for the Late encoding period. In Experiment 2, the average number of cue trials included in the analysis was 124.71 (range: 26–144) for Early encoding and 124.29 (range: 33–143) for Late encoding, and 29.79 (range: 25–32) for fillers in the Early encoding and 29.51 (range: 16–32) in the Late encoding period. LPC amplitude values were analyzed within 600–2000 ms on the basis of visual inspection and previous reports (Friedman and Johnson 2000) after cue presentation during the early and late learning phases at FCz, Cz, and Pz.

TF Analysis

TF was performed per trial using seven-cycle complex Morlet wavelets in 4-s epochs (2 s before cue onset through 2 s after). Changes in time-varying energy (square of the convolution between wavelet and signal) in the studied frequencies were computed for each trial and averaged for each subject. Before performing an overall average, power activity was computed with respect to the baseline of each participant. One participant was removed from the time-frequency analysis in Experiment 1 because she presented power increases greater than 3 SD in all the studied frequencies. Theta power analysis was performed on averaged data from a time window identified based on 2 criteria. First, given that our primary hypothesis was that theta should be enhanced in late learning trials, theta analysis would be around a time point that showed such increment when late and early trials were averaged across subjects. Second, theta effects should be consistent for at least 200 ms (thus capturing at least one full theta cycle in the data). Furthermore, to confirm that the window selected in the theta analysis did not capitalize on chance, a nonparametric two-stage randomization process was used, which also allowed us to account for multiple testing (Blair and Karniski 1993). At the first level, 0–2000 ms theta power data was binned (average of 20 ms data points) and a bin-to-bin paired *t*-test (thresholded at $P < 0.05$, one tail) was used to assess which and how many consecutive time bins (minimum of 2 bins) exhibited significantly higher theta power between conditions throughout the epoch. To correct for multiple comparisons that may potentially result in false positive results, we employed a nonparametric statistical method based on cluster-level randomization testing to control the family-wise error rate. Each permutation run shuffled the assignment of the conditions randomly for each subject. Statistical values larger than a threshold ($P = 0.05$) were selected and clustered into connected sets on the basis of temporal adjacency (Groppe et al. 2011). The observed cluster-level statistics were calculated based on the *tmax* permutation approach that sets a *t* threshold (with an alpha level of 5%), extracted from randomized testing after data have been permuted 5000 times.

Learning, LPC, and Theta Curves

The learning curve was computed by calculating the percentage of correct choices in sliding trial windows of 20 trials shifted in steps of one trial. The LPC and theta curve were obtained by computing the mean LPC over all 20 trials in each trial window used to compute the learning curve. LPC curve was calculated from ERP amplitude data. The 4–6 Hz theta power values used for this analysis were not baseline corrected, thus avoiding variation throughout theta power values over the task being driven by learning-derived baseline differences at the theta band (Guderian et al. 2009). Theta power was then averaged over the selected time window defined in the previous analysis, and the resulting values were *z*-transformed across all trials. To match EEG data to behavioral response at the trial level individually, all trials were included in this analysis but any participant showing a normalized LPC amplitude or theta power in at least 1 data point exceeding 3 SD from the mean was excluded.

Three participants from Experiment 1 and 3 from Experiment 2 were not included in this analysis based on the aforementioned criteria.

Results

Experiment 1

Behavioral Performance

All participants successfully learned and retained the trained associations (Fig. 1C). During encoding, participants' ability to choose the association pair correctly increased greatly during the early encoding phase, and this was reflected in their ability to correctly respond to the first test for trained pairs (mean = 77.76%; SD = 10.55%). Participants further improved during the late encoding period, which was reflected as an incremented accuracy on the final test (mean = 90.84%; SD = 8.13%) (Fig. 1C), thereby indicating that participants' learning of paired association continued throughout the task. In contrast, participants' showed a poorer ability to generalize during the task, although, they still showed improvement over the course of the task, an effect that was more pronounced during the late learning period (early test: mean = 52.30% SD = 15.52%; late test: mean = 65.81%; SD = 17.54%). A repeated measures ANOVA, including time (early and late test) and type of learning (inferred and trained associations) as the within-participant factors, confirmed that participant accuracy improved between initial and late tests (main effect of time: $F(1,36) = 66.92$, $P < 0.001$) and that the accuracy was generally higher for the paired trained associations than for novel conjunction pairs ($F(1, 36) = 134.61$, $P < 0.001$). Participant accuracy on the late test for trained pairs ($t(36) = 30.5$, $P < 0.001$) and generalization ($t(36) = 5.5$, $P < 0.001$) resulted in significantly above-chance scores. Interestingly, as in similar experimental designs (Shohamy and Wagner 2008; Zeithamova and Preston 2010), large individual differences in generalization performance were observed in the task (mean = 65.81%, STD = 17.5%), indicating that, on average, participants were able to exploit the overlap in encountered associations but that they differed in their ability to do so.

Neural Dynamics During the Course of Encoding

As each generalization trial relates to a series of encoding phase events, we examined whether the increase in magnitude of activation from early to late encoding correlated with subsequent accuracy on the generalization probes (a similar approach was used by Shohamy and Wagner 2008).

Thus, because participants' memory accuracy effectively increased during the task, we reasoned that ERPs and neural oscillations supporting memory formation should be reflected when EEG data from the late encoding was compared with EEG data from the early encoding period. More importantly, we hypothesized that ERP differences would be observable mainly as LPC and that differences in neural oscillation would be centered at the theta band. In line with these predictions, the ERP analysis showed a clear amplitude increase of LPC during the late encoding period (Fig. 2A) (repeated measures ANOVA, $F(1, 36) = 36.3$, $P < 0.001$). LPC increased during encoding, initiated at around 600 ms and sustained during a long period lasting through the encoding interval (~2000 ms). In addition, and confirming our hypothesis, differences in spectral power between the early and late encoding period were centered at the theta band (4–6 Hz) over fronto-central scalp regions which appeared at around 1000–1300 ms after cue onset (Fig. 2B). A cluster-based permutation test confirmed such window of analysis represented a good estimate of the theta power differences between these conditions (see Fig. 2B). However, despite being clearly observable, the theta power increase between encoding periods did not reach statistical significance (repeated measures ANOVA, $F < 1$).

LPC and Theta Rhythm at the Individual Level

Having found significant effects for LPC but not for theta responses at the group level led us to question whether these neural markers might, in fact, parallel the behavioral observation that despite participants' being generally able to perform accurately when tested for trained pairs ($N = 35$ out of 37, Binomial test), not all of them were able to reach above-chance performance on the final generalization test ($N = 14$ out of 37, binomial test). To test this hypothesis, we split the participants into 2 groups. We selected the first and last quartile of the sample based on the accuracy in the final test. Importantly, as the aim of this testing was to look for an effect associated solely with the generalization process, we formed the subgroups with the restriction that, between them, there were no differences in their accuracy for trained associations. This yielded "good" ($n = 11$) and "poor" ($n = 11$) generalizers (Fig. 2C), who, despite being similar in their memory accuracy for trained associations (good, 94% ± 7% and poor, 93% ± 4%; time × group, $F(1,20) = 1.173$, $P = 0.292$; group comparison at early: $t(20) = 0.28$, $P = 0.78$ and at late encoding: $t(20) = 1.43$, $P = 0.16$), markedly differed in their ability to generalize on the final test (good 81% ± 8% and bad 51% ± 9%; time × group, $F(1,20) = 9.51$, $P < 0.01$). Post-hoc 2 sample Student t-test showed that the 2 groups differed only in the generalization performance in the late ($t(20) = 8.05$, $P < 0.001$) but not the early test ($t(20) = -0.655$, $P = 0.52$), thereby confirming that generalization performance difference was driven by the encoding process during the task and could not be attributable to a difference in accuracy already appearing at the very beginning of the encoding stage.

Having homogenized participants' subsamples by their ability in trained pairs but differing in their generalization performance, we next examined whether theta activity, but not LPC, differed between them. Critically in this test then, theta power differences between groups should be seen only on late encoding trials, providing strong support for the notion that theta differences may specifically underlie the formation of across-episode memories. Indeed, ANOVA revealed a time × group interaction for theta ($F(1,20) = 8.90$, $P < 0.001$) but not for LPC ($F(1,20) = 1.156$, $P = 0.29$), which showed no significant effect at the group level ($F(1,20) = 0.72$, $P = 0.79$) (Fig. 2C and D). Follow-up t-test comparisons confirmed that theta differences between groups occurred on late ($t(19) = 2.37$, $P < 0.05$) but not early encoding trials ($t(19) = -0.77$, $P = 0.45$), thereby confirming that individual differences in generalization were specifically linked to variations in neural oscillations at theta range during encoding.

Differential LPC and Theta Rhythm Evolvement

Next, we sought to examine whether LPC and theta responses emerged differently throughout the task. We hypothesized that in the event that the 2 neural mechanisms were functionally dissociated in integrative encoding, they should show different patterns of evolvement over the course of the task. Hence, the formation of across-episode memory representations required the existence of discrete yet overlapping memories being retrieved individually, so that relational inferences could be generated without compromising the nature of the existing memory

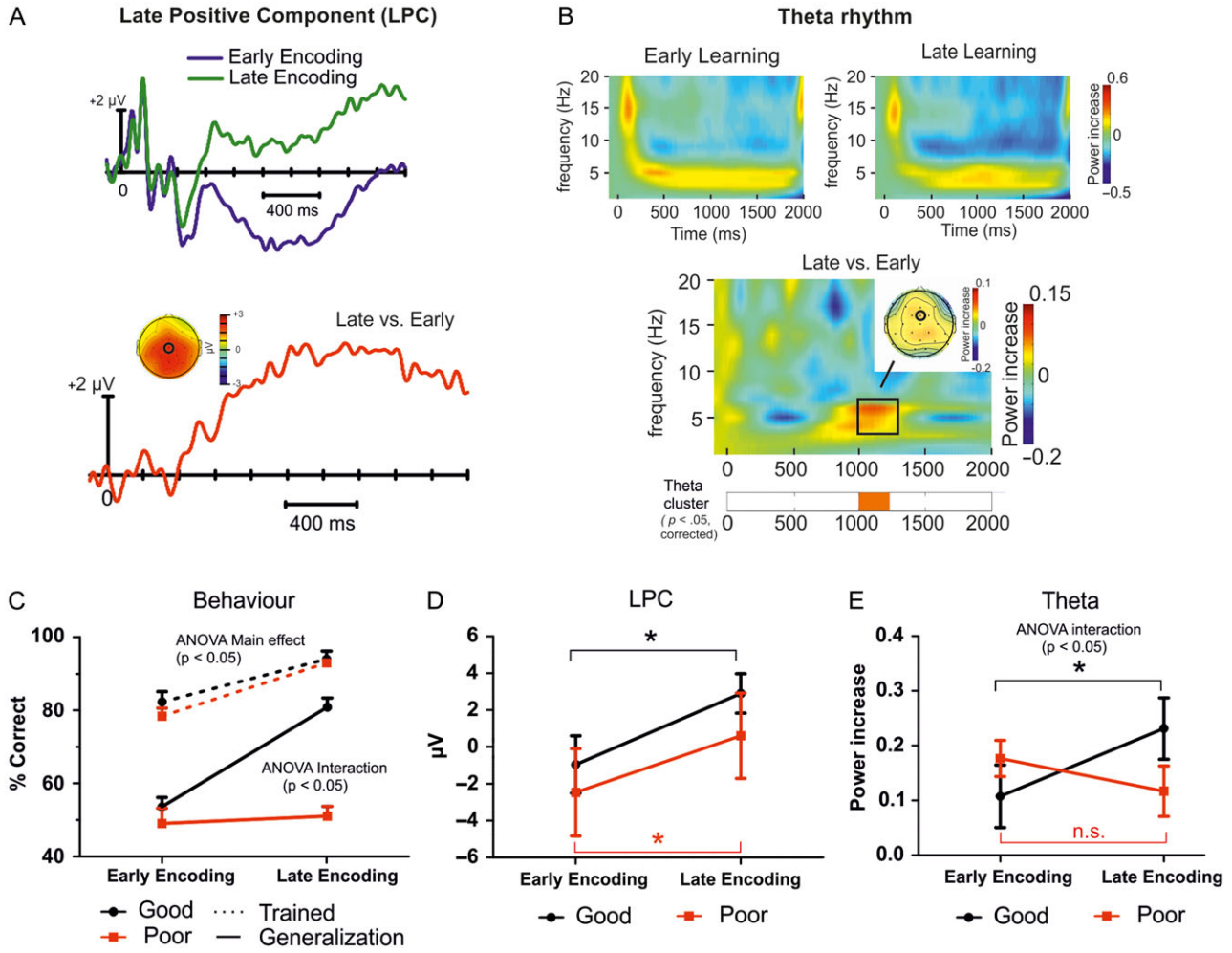

Figure 2. Neural events at cue appearance during the encoding period. (*A*) Group-averaged ERP waveforms at Cz electrode (circled in black) for early and late learning trials. An LPC emerged when comparing late versus early encoding trials. (*B*) Group-averaged changes in spectral power for early and late trials at FCz electrode (circled in black). A power increase in the theta band was observed when late learning trials were compared with early learning trials. A cluster-based permutation test implemented throughout the entire encoding time window (0–2000 ms) identified a significant theta (4–6 Hz) cluster ($P < 0.05$; corrected for multiple comparisons) within the selected time window of analysis. (*C*) We split the participants into two groups. Participants were selected according to the first and last quartile of the sample based on their generalization performance in the final test. (*D*) Good and Poor generalizers' ERP averaged for early and late encoding trials. (*E*) Good and Poor generalizers' theta power changes for early and late encoding trials. *$P < 0.05$ and n.s., $P > 0.05$. Error bars in (C–E) indicate standard error of the mean.

traces (Cohen and Eichenbaum 1993; O'Reilly and Rudy 2001). To address this question, we first sought to investigate the temporal evolvement of LPC and theta by calculating the correct percentage and standardized LPC amplitude and theta power over sliding windows of 20 trials shifted in steps of 1 trial (Tort et al. 2009). This analysis revealed a different pattern of task-related evolvement of LPC and theta (Fig. 3A). Thus, LPC increased gradually throughout the encoding period while theta power remained unchanged during the first half of the encoding period after which it suddenly increased in magnitude, and then increased until the end of the task. To test this statistically, we subdivided the trials into 4 small blocks, and computed the increase/decrease, which can be quantified with the first temporal derivative, of the last half of the trials compared with the first half of trials, thereby providing a measure of degree of discontinuity or change within each block. The results of this analysis would be indicative of the type of growing function underlying the emergence of LPC and theta power over the task. Figure 3B shows the different changes in the activity in the different blocks for both LPC and theta: while LPC presented positive values in all the blocks, theta activity showed an increase in activity only at the third block. Corroborating this differential change, a repeated measures ANOVA, with activity (LPC or theta) and blocks as within factors, showed significant interaction ($F(3,96) = 2.8$, $P < 0.05$) and a significant main effect ($F(1,32) = 5.1$, $P < 0.05$). The analysis of each component revealed that, while LPC amplitude did not show significant differences among blocks (block effect, $F(3,96) = 0.96$, $P > 0.4$), it did in the case of theta activity (block effect, $F(3,96) = 2.7$, $P = 0.05$), with the third block being significantly higher than others (first block, $t(32) = 2.83$, $P < 0.01$; second block $t(32) = 2.45$, $P < 0.05$; fourth block $t(32) = 1.8$, $P = 0.08$). Thus, these findings reveal that constant LPC' growth was maximal at the beginning of the task. In contrast, theta power increased only after half of the task was accomplished.

The differential pattern that evolved in LPC and theta corroborated our initial prediction that the 2 neural responses would emerge differentially over the course of the task. However, this raised the important question as to what extent LPC but not theta oscillations could reliably index the course of

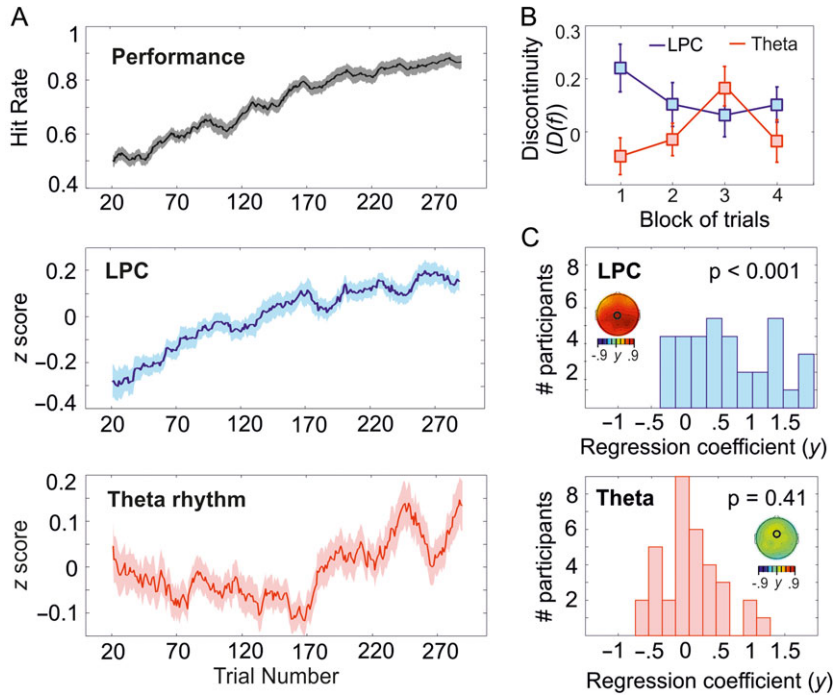

Figure 3. LPC and theta rhythm during learning. (*A*) (top) Behavioral learning curve computed by using a sliding window of 20 trials (averaged proportion of correct responses). Thin lines represent the group-averaged value whereas shaded colors indicate standard error of the mean. (middle) Group LPC-associated learning curve. Note that the behavioral and LPC curves are modulated almost exactly on time. (below) Group-averaged theta power-associated learning curve. Note that, in contrast to LPC, theta emerged abruptly and after ~half the encoding was accomplished by the participants. (*B*) First derivative results calculated from four different blocks of trials throughout the task. The data showed the extent to which the second and first half of the trials for each block differed (i.e., first derivative). (*C*) Histogram of the participants' regression coefficients separately for LPC and theta. *P* values resulted from testing (Student *t*-test) whether the group regression estimates differed statistically from 0. Also added in each scalp distribution of the regression estimates averaged across participants resulting from linear regression computation between LPC and theta oscillations with behavioral responses during learning. Black circles indicate the electrode analyzed.

participants' ability to retrieve individual memories independently of their ability to generalize. Indeed, this prediction remained unanswered in previous analyzes from which only theta changed according to the participants' ability to generalize. To explore this possibility we performed a regression analysis at the individual level using LPC as dependent variable and behavioral choice accuracy as independent measure. If LPC scaled according to participants' behavioral memory accuracy over encoding, then the slope of this relationship would be positive and different from 0. Indeed, this was the case for the LPC ($t(32) = 6.09$, $P < 0.001$) (see Fig. 3C for regression values over sensors for the distribution across participants). Note that the regression was not significant when the same analysis was performed as a control on ERP data from the same electrode but on an earlier time window (i.e., 200–500 ms; $t(32) < 1$), thus lending weight to the argument against the idea that LPC amplitude in this analysis reflected a large effect of trial/time. Importantly, regression analysis with theta and behavioral accuracy did not reach significance when tested against 0 (i.e., reflecting no statistical linear relation between variables) ($t(32) = 0.84$, $P > 0.4$) and was significantly lower than regression values obtained between LPC and choice accuracy ($t(32) = 3.94$, $P < 0.001$). These results were similar for both good and bad generalizers, so that regression analysis between LPC, but not theta, and choice accuracy were significantly different from 0 for both groups (LPC and behavior accuracy for good generalizers $t(10) = 5.1$, $P < 0.001$; for bad generalizers $t(8) = 3.44$, $P < 0.01$; theta and behavior accuracy for both groups $t < 1$) and the regression did not differ between groups at the LPC level ($t(18) = 1.78$, $P = 0.09$). Altogether, these results provide support for the notion that the progress of associative memory formation is associated with neural responses tightly linked to amplitude variations at the LPC level, that this link can be found at the individual level and extends to the relationship between associative memory performance and LPC, and that the variation across individuals cannot be explained by their ability to generalize.

Experiment 2

In Experiment 2, we included several filler items throughout the encoding period to examine the extent to which LPC and theta effects seen in the previous experiment might reflect other cognitive processes (e.g., attention) or might be related to general confounding factors (e.g., fatigue or practice) due to the task structure and analysis (i.e., early vs. late encoding). If this was the case, we would expect LPC and theta response to fillers to be similar to those induced by cue trials. To test against this possibility we compared LPC and theta response changes between early and late encoding periods and between these 2 trial types.

Behavioral Performance

Despite having included filler trials throughout encoding, behavioral performance in Experiment 2 fully replicated the effects seen in Experiment 1. All participants successfully learned and retained the trained associations. Participants' ability to correctly respond to the first test for trained pairs was again high (mean = 75.08%, SD = 11.02%) and increased further on the final test (mean = 86.78%, SD = 11.59%). As in Experiment 1, participants' showed a poorer ability to generalize during the task, although they still showed improvement

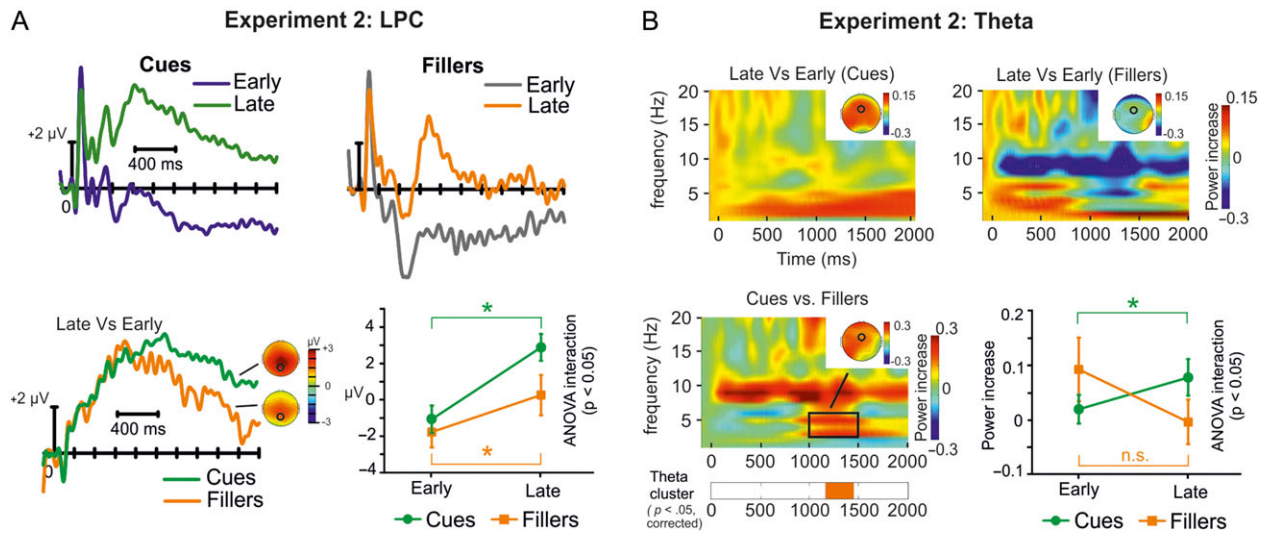

Figure 4. LPC and theta rhythm in Experiment 2. (*A*) Group-averaged ERP waveforms at Pz electrode (circled in black) for early and late learning cue and filler trials. A LPC emerged when comparing late versus early encoding trials but amplitude was much higher in the cue trials. (*B*) Group-averaged changes in spectral power at FCz electrode (circled in black) for early and late cue and filler trials. A power increase in the theta band was observed when late learning trials were compared with early learning trials only in the cue trials. Theta power induced by cues and fillers differed only at late stages of encoding. A cluster-based permutation test implemented throughout the entire encoding time window (0–2000 ms) identified a significant theta (4–6 Hz) cluster ($P < 0.05$; corrected for multiple comparisons) within the selected time window of analysis. *$P < 0.05$ and n.s., $P > 0.05$. Error bars indicate standard error of the mean.

over the course of the task (early test: mean = 53.03%, SD = 13.42%; late test: mean = 62.37%, SD = 15.37%). A repeated-measure ANOVA confirmed that participants' accuracy improved between initial and late tests (main effect of time: $F(1,32) = 28.69$, $P < 0.001$) and that the accuracy was overall higher for the trained associations than for novel conjunction pairs ($F(1,32) = 92.43$, $P < 0.001$). Participants' accuracy on the late test for trained pairs ($t(32) = 17.96$, $P < 0.001$) and generalization ($t(32) = 4.55$, $P < 0.001$) resulted in a significantly above-chance level.

LPC and Theta Effects Do Not Reflect Task Structure Demands

The ERP analysis at Pz electrode (where the effects were shown to be maximal in this experiment; see also Fig. 2*A*) revealed that, although LPC amplitude was greater in response to cues than to fillers (main effect of cue: $F(1,32) = 13.50$, $P < 0.01$), it increased over the course of encoding to both filler and cues (main effect of time: $F(1,32) = 34.15$, $P < 0.001$), and the amplitude increment was more pronounced in late cue trials (ANOVA interaction time × trial type: $F(1,32) = 4.18$, $P < 0.05$) (Fig. 4*A*). Follow-up paired *t*-test showed that LPC differences between cue and filler trial types were more pronounced in the late encoding ($t(32) = 2.66$, $P < 0.05$); early encoding period ($t(32) < 1$). In addition, and replicating the results from Experiment 1, a clear power increase centered at theta (4–6 Hz) was observed between early and late encoding periods in cue trials. Importantly, this theta increase was not evident between early and late period in filler trials. The early versus late contrast between cues and filler trials showed that theta power increase (4–6 Hz) was consistent across subjects within 1000–1500 ms (Fig. 4*B*). Notably, the cluster-based permutation test corroborated that such window of analysis represented a good estimate of the theta power differences between these conditions (see Fig. 4*B*). This effect was confirmed statistically with a repeated measures ANOVA that showed a significant interaction effect (time × trial type: $F(1,32) = 5.53$; $P < 0.05$). A trend toward significance was revealed when comparing theta responses between cues and fillers in the late period ($t(32) = 1.97$, $P = 0.06$) while theta did not differ between them at early stages of learning ($t(32) = -1.41$, $P > 0.1$).

Finally, early versus late comparison for filler trials also helped in clarifying the extent to which activity in other frequency bands played a role in memory generalization processes during encoding. For instance, Figure 4*B* shows a prominent alpha decrease in late encoding period in filler trials that is not that apparent in early versus late comparison in cue trials. The alpha power effect in filler trials was confirmed statistically by a significant interaction stimulus type × time interaction (including alpha power averaged over 300–2000 ms stimulus onset at FCz; $F(1,32) = 4.34$, $P < 0.05$). Post-hoc paired *t*-test corroborated that alpha decrease was significant for fillers (early vs. late; $t(32) = 2.62$, $P < 0.05$) and that the power change was at the trend level for cue trials ($t(32) = 1.79$, $P = 0.08$). For completeness, we compared alpha power changes in Experiment 1 (early vs. late) and found that the decrease was statistically significant ($t(36) = 2.64$, $P < 0.05$). Thus, although alpha power changes occurred throughout encoding in Experiments 1 and 2, data from Experiment 2, which showed that the alpha decrease was mostly observed in response to filler trials, suggested that differences in alpha power between early and late trials may reflect general differences during task performance that cannot be attributed to processes of memory generalization (e.g., attention (Klimesch et al. 2007)).

LPC and Theta Rhythm at the Individual Level

Findings in experiment 1 revealed that the specificity of the theta activity to memory generalization was further supported by splitting the participant sample into good and poor generalizers. We asked, then, whether similar results were observed in Experiment 2 when extended to filler trials too. Thus, as in Experiment 1, participants were split into a group of "good" ($n = 10$) and a group of "poor" ($n = 10$) generalizers who, despite showing similar memory accuracy for trained associations (good, 88% ± 8% and poor, 89% ± 10%; time × group, $F(1,18) = 0.35$, $P = 0.56$; group comparison at early: $t(18) = -0.49$, $P = 0.62$, and at late encoding: $t(18) = 0.64$, $P = 0.7$), markedly differed in their ability

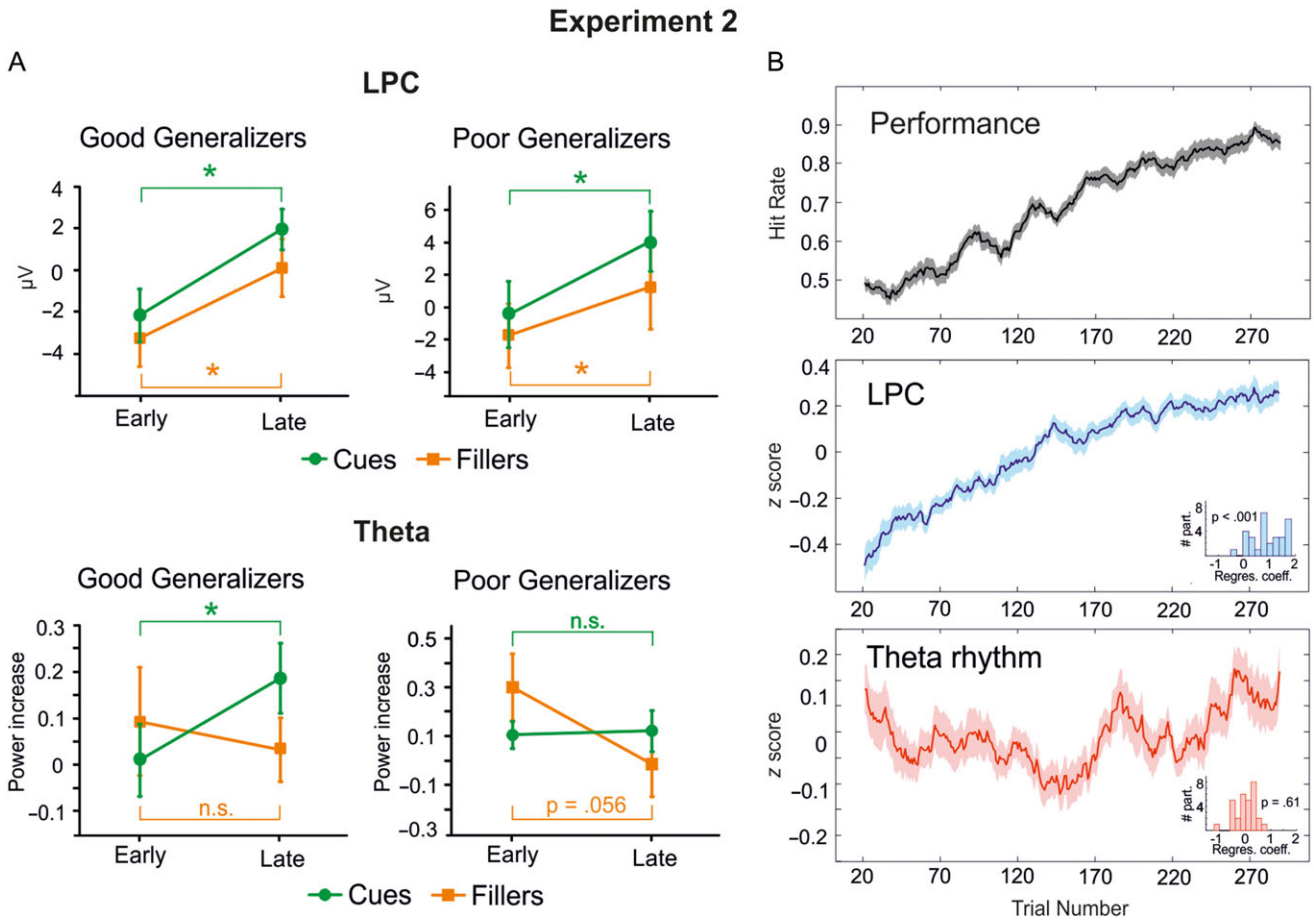

Figure 5. LPC and theta rhythm for the "Good" and "Poor" generalization participants and group learning-associated curves in Experiment 2. (*A*) Good and Poor generalizers' ERP averaged and theta power for early and late encoding trials. (*B*) (top) Behavioral learning curve and (middle) Group LPC-associated learning and (below) Group-averaged theta power-associated learning curve. Thin lines represent the group averaged value whereas shaded colors indicate standard error of the mean. Curves are calculated as in Figure 3A. Histogram of the participants' regression coefficients separately for LPC and theta are also plotted. *P* values resulted from testing (Student *t*-test) whether the group regression estimates differed statistically from 0. *$P < 0.05$ and n.s., $P > 0.05$. Error bars in (A) indicate standard error of the mean.

to generalize on the final test (good 76% ± 7% and poor 57% ± 10%; time × group, $F(1,18) = 4.47$, $P < 0.05$). Post-hoc 2 sample Student *t*-test confirmed the 2 groups differed only in the generalization performance in the late ($t(18) = 3.99$, $P < 0.001$) but not the early test ($t(18) = 0.97$, $P = 0.34$).

Having homogenized participants' subsamples in Experiment 2 by their ability in trained pairs but differing in their generalization performance, we next examined whether theta activity, but not LPC, differed between them specifically in cue but not in filler trials. To test this possibility statistically, we ran separate repeated-measure ANOVAs for LPC and theta measures. This analysis confirmed that LPC increased during the task for the 2 groups in a similar manner (main effect of time: $F(1,18) = 36.01$, $P < 0.001$; interaction time × group: $F(1,18) = 0.01$, $P > 0.9$), and that LPC amplitude was greater for cues than for filler trials in both groups (main effect of cue: $F(1,18) = 10.19$, $P < 0.01$; interaction cue × group: $F(1,18) = 0.28$, $P > 0.5$) (Fig. 4C).

We next assessed whether the theta increase between early and late learning phases was specific to cue trials in the good but not the poor generalizers. The ANOVA on theta activity revealed a significant type × time interaction ($F(1,18) = 11.48$, $P < 0.01$), a time × group interaction ($F(1,18) = 4.53$, $P < 0.05$), although the interaction type × time × group failed achieve significance ($P > 0.1$). To try to further elucidate the source of such differences, separate ANOVAs for each group were performed and their results confirmed the 2 groups showed a significant cue × time interaction effect (Good generalizers: $F(1,9) = 5.62$, $P < 0.05$; Poor generalizers: $F(1,9) = 6.04$, $P < 0.05$), although theta increments to cue trials seemed to be specific to good generalizers only (see Fig. 5A). We assessed this by implementing follow-up paired *t*-test analysis which confirmed that good, but not poor, generalizers showed a significant increase in theta activity in cue trials between early and late learning trials (good: $t(9) = -5.50$, $P < 0.001$; poor: $t(9) = -0.27$, $P > 0.2$). Theta activity did not differ between early and late phases for filler trials in good generalizers ($t(9) = 0.67$, $P > 0.5$), although a trend towards significance was found in poor generalizers ($t(9) = 2.19$, $P = 0.056$). All in all, these results are consistent with findings in Experiment 1 that theta increase to cues in the late learning phase is specifically associated with individuals who performed well on the generalization test.

LPC, but Not Theta Rhythm, Fits to Individual Memory Performance at the Trial Level

Finally, we examined whether LPC and theta responses to cues throughout the task fitted to individual memory performance at the trial level in Experiment 2. Thus, as in Experiment 1, we

first calculated the correct percentage and standardized LPC amplitude and theta power over sliding windows of 20 trials shifted in steps of 1 trial. The results of this analysis are displayed in Figure 5B. We then performed a regression analysis at the individual level using LPC as dependent variable and behavioral choice accuracy as independent measure to assess, as in Experiment 1, whether LPC scaled according to participants' behavioral memory accuracy over encoding. Indeed, this was the case for the LPC ($t(29) = 7.80$, $P < 0.001$) (see Fig. 5B) but not for theta ($t(29) = 0.41$, $P > 0.6$) which showed significantly lower regression values than with LPC ($t(29) = 6.06$, $P < 0.001$). Altogether, these results replicate findings from Experiment 1 and provide support for the notion that the progress of associative memory formation is associated with neural responses linked to amplitude variations at the LPC level.

Discussion

In the current EEG study, we show that integrative encoding—the ability to form individual and across memory representations during online encoding—is supported by 2 distinct neurophysiological responses. A slow ERP component increased gradually during encoding and fit to a trial level memory measure for individual episodes. Neural oscillatory responses in the theta range (4–6 Hz) emerged later during learning and predicted participants' generalization performance in a subsequent test. These results suggest that integrative encoding requires the recruitment of 2 separate neural mechanisms that, despite their co-occurrence in time, differ in underlying neural dynamics, reflect different brain learning rates, and are supportive of the formation of opposed memory representations, individual versus across-event episodes.

A core property of integrative encoding is that by recalling past events during new experiences, connections can be created between newly formed and existing memories (Shohamy and Wagner 2008). Thus, integration of new information into an existing memory depends on elemental encoding of the initial memory such that it can be reactivated when the overlapping element is encountered again in the subsequent episode, without causing interference with the stored individual elements (Norman et al. 2005). Therefore, while it is important to prevent interference during encoding, it is also critical to have an ongoing ability to access discrete representations for retrieval given that this, in turn, can lead to encoding of the distinct discrete events into an integrated representation. Our findings that task-related LPC amplitude varied according to participants' performance at the trial level suggests that this ERP reflects, at least partially, the output of retrieval operations. Interestingly, an LPC-like component has been shown to indicate the success of memory retrieval operations (Düzel et al. 1997; Rugg and Curran 2007). These studies confirmed the appearance of LPC in retrieval tasks to be hippocampus-dependent (Düzel et al. 2001) and to reflect the reinstatement of "content-specific" memory information (Johnson et al. 2008; Jafarpour et al. 2014). Here, we propose that, during integrative encoding, the access of discrete memory episodes and their reinstatement, allowing such memory to be integrated into a distinct yet overlapping memory input, are reflected as amplitude modulations in the LPC.

According to theoretical proposals, encoding of new information without interference from previously encoded information requires transitions between encoding and retrieval states (Hasselmo et al. 2002), which may be enhanced by modulatory changes in synaptic transmission during the theta cycle in the hippocampus (Wyble et al. 2000; Molyneaux and Hasselmo 2002). Our findings that EEG theta activity during encoding only explained the participants' ability to generalize support this view. However, and because theta activity in our study resulted from scalp EEG recordings, it is likely that theta modulations also engage, at least partially, the activity of neocortical regions.

Indeed, animal (Jones and Wilson 2005; Siapas et al. 2005; Benchenane et al. 2010) and human (Guitart-Masip et al. 2013; Fuentemilla et al. 2014) studies show converging evidence that theta oscillations are a physiological conduit through which the coordinated activity of hippocampal and neocortical regions takes place. The resulting dialog would drive plastic changes in short- and long-range synaptic connections and contribute to creating widespread integrated representations of items and experiences, selecting and retaining the information that is most valuable for adaptive behavior (Benchenane et al. 2010). This is especially important for inferential learning, during which the extraction of new knowledge extends beyond direct experience to anticipate future inferential judgments about the relationships between experiences (Cohen and Eichenbaum 1993; Eichenbaum 1999).

In fact, recent studies have led to a proposal of how the hippocampus forms and replays memories and how the prefrontal cortex engages representations of the meaningful contexts in which related memories occur, thereby promoting generalization (Preston and Eichenbaum 2013). This model assumes that the hippocampus is essential for forming cohesive memories of individual events within the context in which they occurred (Davachi 2006; Diana et al. 2007). Critically, a part of the hippocampus sends outputs to the medial prefrontal cortex (mPFC) which accumulates information about the context of interrelated memories. In turn, the mPFC sends back projections to the hippocampus thereby biasing the retrieval of event information (Xu and Sudhof 2013). Given the strong preference of the mPFC and the hippocampus to functionally interact during learning via theta synchronization (Siapas et al. 2005), it is reasonable to assume that the emergence of theta activity may support the ability to create contextual or abstract representations that link related memories and then use these contextual representations to retrieve the memories that are relevant within a given context.

Although theta oscillations in our data may reflect the effective mPFC-hippocampal interaction to support the integration of overlapping memories, the fMRI approach used by Shohamy and Wagner (2008) demonstrates that in fact our ability to generalize is supported by the dynamic interaction between midbrain and hippocampal regions. Based on the suggestion that a functional loop between the midbrain (VTA) and the hippocampus serves to enhance episodic memory for novel events (Lisman and Grace 2005), the authors argued that whenever the memory reactivation features of an event do not coincide with a current input, the mismatch signal originating in the hippocampus upregulates midbrain dopaminergic feedback to the hippocampus. The consequence of this is to increase the probability of encoding the present and prior event features into an integrated representation. We propose that this possibility is not incompatible with the suggestion that theta activity found in the current study engages the recruitment of mPFC-hippocampal network. Thus, a recent study in rats showed that neuronal activity in the mPFC, the hippocampus, and the midbrain ventral tegmental area (VTA) during memory processes is coordinated by a 4 Hz oscillation (Fujisawa and Buzsáki 2013). This suggests that during integrative encoding, the triple interactive activity of mPFC-VTA-hippocampus would mediate the need to hold simultaneously different but overlapping memory representations and the recruitment of the mesolimbic dopaminergic system necessary for establishing the formation of relational memory

representations whenever a mismatch between current and previous memory elements is encountered.

In summary, the present data demonstrate the existence of two different EEG-based neural mechanisms that track the ability to carry out integrative encoding. The current findings corroborate previous investigations showing that memories for distinct experiences are rapidly integrated during encoding (Shohamy and Wagner 2008) and extend them by providing the time course and the neural dynamics that account for this process during learning. Furthermore, the opportunity to investigate these two neural mechanisms with scalp EEG recordings represents a valuable contribution to clinical environments. Thus, the simple placing of a few EEG sensors, even at the ambulatory level, would allow a fine-grained exploration in neurological patients of basic neural mechanisms that are very relevant in terms of the adaptive nature of memory, whereby memory representations are constructed to anticipate, and successfully negotiate, future judgments.

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