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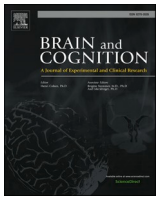

# Spatio-temporal theta pattern dissimilarity in the right centro-parietal area during memory generalization

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ABSTRACT

Generalization across past events may guide our action in novel situations. Although generalization is a fundamental memory process, its neural underpinnings are not fully understood yet. In the present experiment, we combined Electroencephalography (EEG) with multivariate representational similarity analysis (RSA) to examine in particular the role of spatio-temporal patterns of theta oscillations known to be important for associative memory processes, in memory generalization. We recorded EEG while healthy participants ($n = 56$) performed an acquired equivalence task. In this task, participants first acquired multiple associations among antecedent and consequent stimuli before they were required to transfer the acquired knowledge to novel stimulus pairs, thus probing memory generalization. Our behavioural data indicated that participants learned the initial associations well and transferred these associations successfully to novel test stimuli, demonstrating successful memory generalization. Our neural data revealed that, compared to mere memory retrieval, generalization was associated with significantly increased pattern dissimilarity of theta activity in the right centro-parietal area (electrodes *P4* and *P6*). This pattern was specific to theta oscillations and not observed in other frequency bands. Our findings suggest an important role of theta oscillations in memory generalization, potentially serving the reactivation and integration of distinct events that enable the generalization across experiences.

## 1. Introduction

Although no two events are the same, experiences often overlap in their content. Such overlaps provide the opportunity for generalizing across them. Generalizing across experiences is a fundamental cognitive process enabling memories to guide our behaviour (Shohamy & Adcock, 2010; Wolosin et al., 2012). Several mechanisms by which memory generalization takes place have been proposed. An integrative encoding account assumes that the basis for generalization is laid during the encoding of discrete events. These events would be integrated into an associative mnemonic network, the dynamic nature of which allows the direct retrieval of relations between events that have never been experienced together (Shohamy & Wagner, 2008; Zeithamova & Preston, 2010). An alternative view holds that memory generalization relies on the flexible expression of memories during retrieval (Eichenbaum, 2000; Cohen & Eichenbaum, 1995). The flexible retrieval of discrete events would enable memory generalization through transitive and associative inference processes (Shohamy & Wagner, 2008; Dusek & Eichenbaum, 1997).

A fundamental question concerns the neural mechanisms underlying the generalization across experiences. Both, integrative encoding of events and flexible expression of memories, are supported by the hippocampus and adjacent cortices. For instance, while the hippocampus encodes memories as discrete events (Kirwan & Stark, 2007; Leutgeb et al., 2007), it is also critical for linking these discrete representations (Borders et al., 2022; DuBrow & Davachi, 2016; Staresina & Davachi, 2009). Moreover, the hippocampus has been shown to be critical for mnemonic inference processes (Zeithamova et al., 2012; Heckers et al., 2004). Recent studies utilizing M/EEG have further shown that the integration of novel events into an existing associative memory network relies on oscillatory activity in the theta range (4–7 Hz; Nicolás et al., 2021; Sans-Dublanc et al., 2017; Backus et al., 2016). Theta oscillations

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are found throughout the whole brain, yet most prominently in frontal-midline regions as well as the hippocampus (Cavanagh & Frank, 2014; Buzsáki, 2002). Theta activity is observed during the formation (Kota et al., 2020; Greenberg et al., 2015; Rutishauser et al., 2010) as well as the retrieval (Pastötter & Bäuml, 2014) of episodic memories alike, suggesting that theta oscillations are linked to the reinstatement of episodic memory representations through feedback projections from the hippocampus to the cortex (Nyhus & Curran, 2010). Accordingly, theta oscillations are thought to act as the "glue" which binds the components of associative memories together (Clouter et al., 2017; Berens & Horner, 2017).

In the context of memory generalization, theta activity has been recently linked to integrative encoding processes (Sans-Dublanc et al., 2017). However, whether theta may also be involved in distinct memory processes at retrieval, during the actual memory generalization, is unknown. To tackle a potential role of theta oscillations during the generalization across past experiences, we employed a previously introduced acquired equivalence paradigm (Myers et al., 2003) to probe memory generalization. In this paradigm, participants first acquired multiple associations between antecedent and consequent stimuli before they were required to transfer (i.e. generalize) the learned associations to novel stimulus pairs. We recorded Electroencephalography (EEG) during initial acquisition and subsequent memory generalization. In order to test whether memory generalization is linked to a (dis-)similar and therefore event-specific pattern of theta activity, we leveraged multivariate representational similarity analyses of theta activity (Nicolás et al., 2021; Estefan et al., 2021). We hypothesized that generalization trials would - compared to simple retrieval trials - be characterized by a distinct and thereby dissimilar pattern of theta activity. In light of previous evidence for gender differences in episodic memory processes (Asperholm et al., 2019; Lewin, Wolgers, & Herlitz, 2001; Herlitz & Rehnman, 2008), we exploratively investigated potential differences between men and women in memory generalization and its neural underpinnings.

## 2. Materials and methods

### 2.1. Participants

Fifty-six healthy, right-handed adults with normal or corrected-to-normal vision (29 women, 27 men; age = 19–32 years, mean = 24.69 years, SD = 3.43 years) participated in this experiment. This sample was part of a larger research project on learning and memory processes and their modulation by stress. Exclusion criteria were checked in a standardized interview and comprised a history of any neurological or psychiatric disorders, smoking, drug abuse, and intake of any prescribed medication. Women were only included if they did not use hormonal contraceptives, and were not tested during their menses. In addition, participants were asked not to eat or drink anything except water within 2 h before the experiment, and not to do any exercise on the day of the experiment. Participants gave written informed consent before testing and received a monetary compensation after completing the study. The study protocol was approved by the local ethics committee of the Faculty for Psychology and Human Movement Sciences at the Universität Hamburg.

A power calculation using G*Power (Faul et al., 2007) indicated that a sample of $n = 54$ is sufficient to detect an effect of $dz = 0.5$ for the within-subject comparison of old and generalization items in the generalization phase (see 2.2.1) with a power of 0.95. The assumed medium-sized effect is based on previous results by Bowman and Zeithamova (2018).

### 2.2. Experimental procedure

After their arrival in the laboratory, participants received information on the experimental procedure and gave written informed consent to participate in this study. Participants were seated approximately 80 cm from a computer screen in a sound-attenuated room, where they were prepared for EEG measurements.

#### 2.2.1. Acquired equivalence paradigm

While EEG was measured, participants completed a computerized version of an associative learning task that has been introduced before to probe memory generalization (Myers et al. 2003; Kluen et al., 2017; Dandolo & Schwabe, 2016). In this task, participants were presented with pictures of differentially coloured fish (consequent stimuli) and pictures of faces (antecedent stimuli; neutral expression, differing in age, sex, and hair colour). The task consisted of four different stages: in the first three stages (acquisition phase), participants acquired successively specific face-fish associations (Fig. 1A). During the fourth stage, participants were required to *transfer* their knowledge to unlearned combinations via generalization (Fig. 1B).

During the acquisition phase, participants saw one individual and two differently coloured fish in each trial. They were asked to indicate by button press on a keyboard which fish belonged to the face presented. Once participants selected a fish, a frame was placed around the fish and feedback was given about the correctness of their answer. The response was marked for 700 ms and feedback was presented for 1.7 s. Across all stages, trials started with a fixation cross (500 ms), and participants had to respond within 2 s. In stage one (*shaping*), participants learned eight associations of fish (antecedent stimulus) and faces (consequent stimulus). Stage two (*equivalence training*) directly followed the first stage. Here, eight new faces were introduced. These new faces were paired with already presented fish forming an equivalence of two of the faces. Importantly, the four faces sharing one fish shared the same sex and hair colour, in order to facilitate equivalence learning. In stage three (*new consequents*), the eight faces from the shaping stage as well as the eight faces from the equivalence training stage were shown again. However, the eight faces from the *shaping* stage were now paired with new fish, so each face could now be associated with two different fish. During each stage, 24 new trials were introduced and presented together with all trials from the previous stages. Importantly, participants received feedback upon their response during the *acquisition* phase, allowing feedback-based learning.

The *acquisition* phase was followed by the critical *transfer* phase. During this phase, all 72 old trials from the previous stages were intermixed with 24 generalization trials. These generalization trials included faces that were introduced in stage two, paired with two fish that were shown in stage three. Now participants had to use the learned equivalences and transfer that knowledge to the generalization trials in order to predict correctly which fish belonged to the shown face. In this *transfer* phase, no feedback was provided.

### 2.3. EEG data acquisition and analysis

EEG was recorded by means of a 64 electrode BioSemi ActiveTwo system (BioSemi B.V.), organized according to the international 10–20 system. EEG data was recorded using a sampling-rate of 1024 Hz, and an online band-pass filter of 0.03 – 100 Hz. External electrodes were placed at both mastoids, approximately 1 cm above and below the orbital ridge of each eye and at the outer canthi of the eyes. Prior to EEG recordings, electrode DC offsets were kept in range of ± 20 ηV with the common mode sense and driven right leg (DRL) electrodes as recording active reference and ground, respectively.

#### 2.3.1. Preprocessing

EEG data from the acquired equivalence task were analysed offline using the FieldTrip toolbox (Oostenveld et al., 2011) as well as custom scripts implemented and processed in MATLAB (The MathWorks). Trials were epoched from −1 to 3 s relative to stimulus onset, re-referenced to the common average of all scalp electrodes and demeaned (based on the average signal of the whole trial). Additionally, a Discrete-Fourier

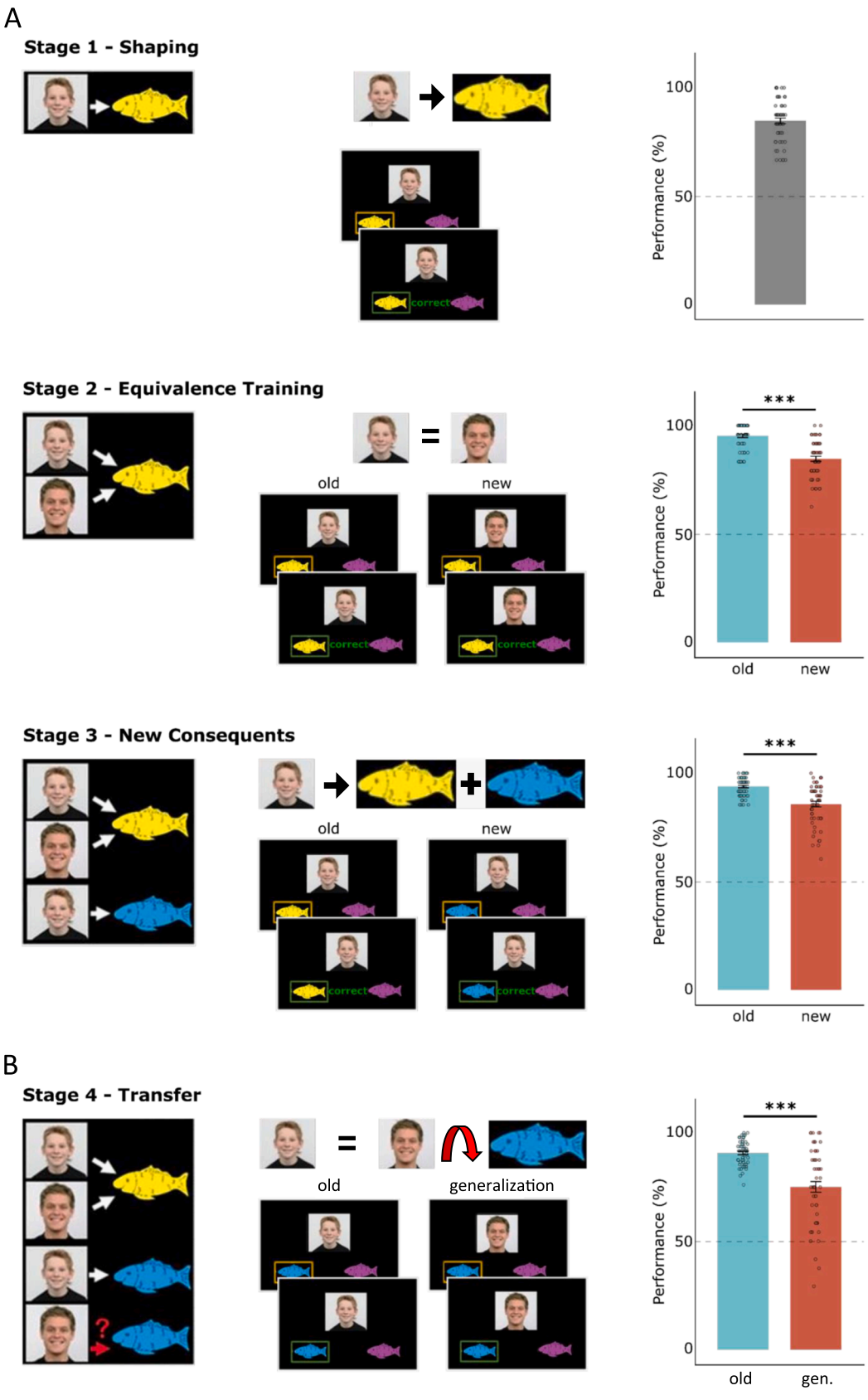


**Fig. 1.** Acquired equivalence paradigm and behavioural performance. (A) The acquisition phase included three subsequent stages during which feedback was provided upon every response. In stage one (shaping), participants were presented stimulus-pairs of antecedent and consequent stimuli. During stage two (equivalence training), 24 new trials were introduced including new antecedent stimuli, which were paired with the same consequent stimuli as stage one trials, forming an equivalence between both antecedent stimuli. In stage three (new consequents), again 24 new trials were introduced, this time adding new consequent stimuli to the already known antecedent stimuli from stage one, so that stage one trials now had two corresponding consequent stimuli. Across all stages of the acquisition phase, trials from the previous stages were presented again. In each stage of the acquisition phase, participants successfully retrieved stimulus-pairs from the previous stages, and also learned the new combinations very well. (B) The acquisition phase was followed by the transfer phase, including only one stage, in which no feedback was provided. Here participants were shown every trial that was presented in the acquisition phase (old trials) and additionally 24 generalization trials. During those generalization trials participants needed to transfer their knowledge of equivalent stimuli from stage two, to the new consequents of stage three trials. Participants were thereby asked to respond to stimulus-pairs they had not learned but could only be solved by a successful generalization across antecedent stimuli. In the transfer phase, old trials from the acquisition phase were remembered very well, and also generalization trials were solved above chance on average, reflecting a successful induction of memory generalization. In all of the stages, participants performed very well, with significantly better performance for old vs generalization items. Bars represent means (±SE); *p <.05, **p <.01, ***p <.001; dashed lines indicate the chance level (50 %).

Transform (DFT) filter was applied at 50 Hz to cancel out power-line noise. Single electrodes that either did not record or revealed constant noise were removed (max. 1 per participant) and interpolated using the weights of its corresponding neighbouring electrodes. To remove extreme noise related to muscle artefacts or external influences, we utilized a threshold-guided semi-automatic detection method (z-value based median filter of 9th order, including a z-value cut-off of 75). Following this procedure, on average 2.71 (±3.11 SD; range: 0–12) of the total 96 *transfer* phase trials as well as 5.87 (±5.05 SD; range: 0–20) of the total 168 *acquisition* phase trials were removed in each dataset. Following artefact rejection, epochs were down-sampled to 250 Hz. Next, we calculated an extended infomax independent component analysis using the 'runica' command (ICA, stop criterion: weight change $\langle 10^{-7}$) in order to identify and reject components related to eye-blinks and other sources of noise. Following a two step-procedure, we first correlated the signal of the horizontal and vertical EOG electrodes with each independent component. Components with a correlation $> 0.9$ were removed immediately; components with a correlation $> 0.6$ were noted for later inspection. In the second step, we identified all remaining components by visual inspection of time courses and corresponding brain topographies. On average 4.42 (±SD: 1.39; range: 2–8) components reflecting electro-ocular activity were removed before back projecting the signals into electrode-space.

#### 2.3.2. Frequency decomposition

The spectral decomposition of EEG data was performed using sliding Hanning windows (2–30 Hz, 1-Hz steps, five-cycle window, interval: −1–3 s relative to stimulus onset). This way we were able to calculate the time–frequency representations with respect to a time window that varies with frequency.

Single trial power estimates were later log-transformed (Smulders et al., 2018; Grandchamp & Delorme, 2011) and baseline corrected (absolute baseline correction −0.5 to 0 s relative to stimulus onset). This procedure was conducted on trials from the *acquisition* and *transfer* phase.

In order to probe the role of theta frequency activity in memory generalization, we in an initial oscillatory power analysis we averaged the time–frequency representations over trials (in both phases), electrodes and time (0 – 2 s relative to stimulus onset). This way we were able to create average frequency spectra for each trial category (old, new). The resulting spectra were later binned according to commonly used frequency definitions (Theta: 4–7 Hz; Alpha: 8–12 Hz; Beta: 13–30 Hz; Low-Gamma: 31–45 Hz; Jasper & Andrews, 1936).

#### 2.3.3. Representational similarity analysis

In order to investigate the distinct neural patterns associated with memory generalization, we leveraged a representational similarity analysis (RSA) on the EEG sensor level. RSA allows the estimation of activity patterns associated with specific events, measuring (dis-)similarity by correlations of neural activity (Nicolás et al., 2021; Estefan et al., 2021; Sommer et al., 2019). RSA can be used flexibly, comparing intertrial-similarity within or across events of interest. These approaches allow us to either investigate distinct (dis-)similarity among trials belonging to the same category, or to estimate the (dis-)similarity across stimulus categories, indicating whether trials of two different categories show an overall (dis-)similar pattern of underlying neural activity. Accordingly, we applied the following RSA *within* each trial category (old, new) as well as *across* both stimulus categories.

First, we quantified the similarity of neural representations *within* each trial category of old and generalization trials of the *transfer* phase separately. We compared epochs of brain activity within all available electrodes of each subject. Using oscillatory theta power, we created representational feature vectors consisting of trial-wise power values of 4 (frequencies; 4 – 7 Hz) × 41 (time points; 0 – 2 s) × 64 (electrodes). Next, we calculated Spearman's correlations of frequency bin power patterns across theta bins between time points of different trials separately for trial categories and electrodes, resulting in a global measure of similarity between trials *within* each category for each electrode site. Spearmans' *rho* values at each time point were Fisher z-transformed for later statistical comparisons. This resulted in *time* × *time* similarity maps for each trial-combination at each electrode for each subject respectively (Fig. 2A). Correlations were calculated within (and not across) electrodes for each trial combination, which allowed later localization of potential effects using i.e., topographical plots. Importantly, we made sure not to correlate the same trial combinations twice, to prevent a biased inflation of the data (i.e., $\text{trial}_a$ was correlated with $\text{trial}_b$, but not the other way around). With this approach, we were able to quantify the representational similarity among trials *within* each trial category (i.e., reflecting whether generalization trials were processed with a (dis-)similar pattern of neural activity).

In a further analysis, we estimated the representational similarity *across* both stimulus categories, by correlating old with generalization trials of the *transfer* phase, again avoiding using trial combinations twice. The resulting similarity maps consisted of Fisher z-transformed *time* × *time* correlation maps reflecting the direct (dis-)similarity of old and generalization trials. Analysis of *cross*-category representational similarity were focussed on trials of the transfer phase, as memory generalization is exclusively probed in this stage. We did not run RSA to compare trials *across* acquisition and transfer phase because "generalization" trials in the transfer phase were fundamentally different from trials in the previous stages, Moreover, a cross phase RSA would have been biased by the novelty (stage 1) and familiarity (stages 2 and 3) of stimuli compared to trials of the transfer phase. As previous evidence suggested a potential role of theta activity during the formation of associative memories and later generalization (Sans-Dublanc et al., 2017), we repeated the oscillatory power as well as time–frequency and RSA (*within*-category) analyses, this time focussing on stimulus-pairs from the acquisition phase.

### 2.4. Statistical analysis

To assess the behavioral performance during the *acquisition phase* we applied a one-way repeated measures ANOVA including the factor stage (3 acquisition stages and transfer stage). Additionally, we used paired samples t-tests comparing performance of old vs new trials in each stage separately. We further used one-sample t-tests to analyse whether performance during all acquisition stages was significantly different from chance (50 %). Behavioural data from the *transfer phase* were analysed accordingly using paired samples t-tests. In order to uncover potential gender effects explorative analysis were employed.

Statistical analyses of whole brain EEG frequency data focussed on the *transfer phase* of the acquired equivalence task because only this phase allowed an assessment of memory generalization processes, which are at the heart of this study. Analyses were restricted to 0–2 s after stimulus onset.

In order to probe the relevance of theta oscillations for memory generalization, binned power-estimates from the averaged frequency spectra were compared using a repeated-measures ANOVA, including the between-subjects factor *stimulus-type* (old, new) and the within-subject factor *frequency* (theta, alpha, beta, gamma).

For the whole-brain time–frequency data, spectral power differences between old and generalization trials in theta frequency range were tested with a dependent sample cluster-based permutation *t*-test (10.000 permutations to correct for multiple comparisons; Maris & Oostenveld, 2007). This approach allows testing for statistical differences while controlling for multiple comparisons, without the need to restrain the analysis to a certain location. The samples were clustered at a level of $\alpha_{\text{cluster}} = 0.01$. Clusters with a corrected Monte Carlo *p*-value $< 0.05$ are reported as significant.

The representational similarity maps from the *within* category RSA were averaged over trials and subsequently contrasted via a dependent sample cluster-based permutation *t*-test. This approach served to

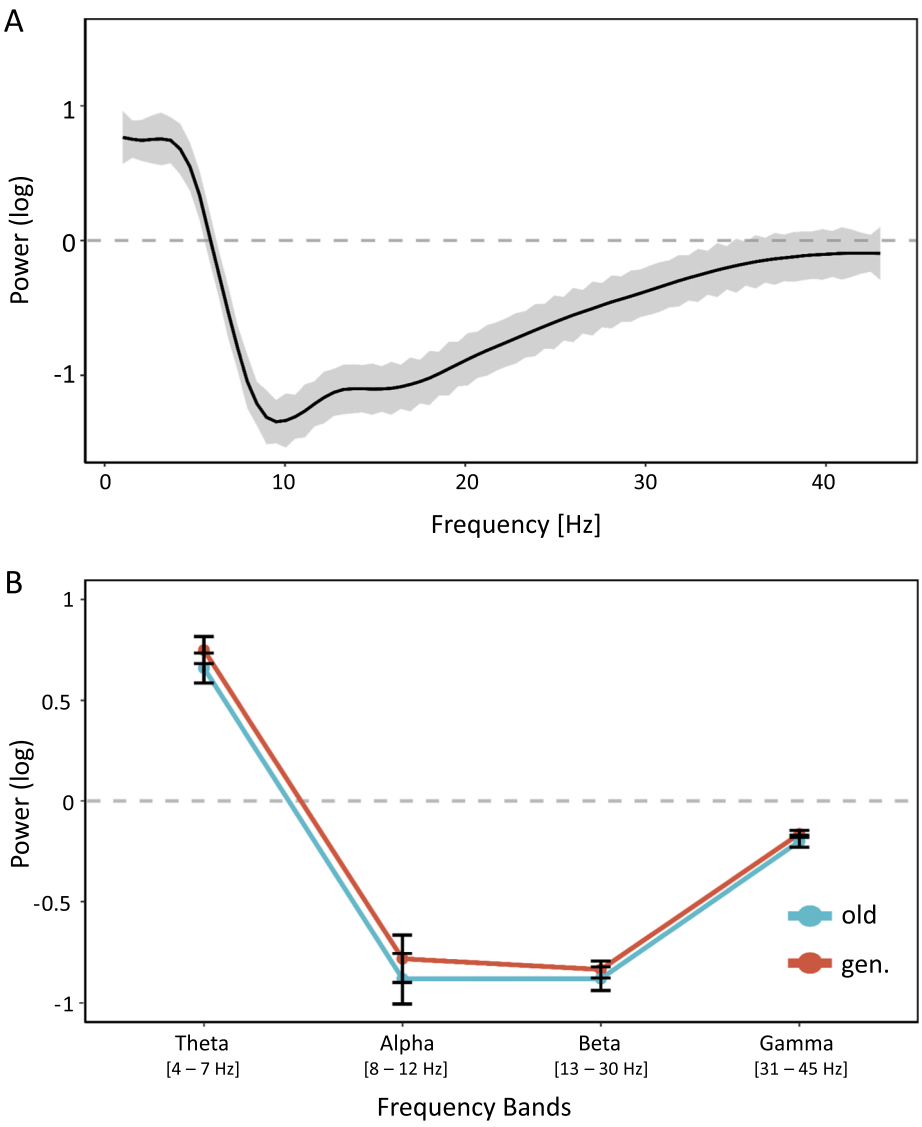


**Fig. 2.** Theta Power increase during memory retrieval (old items) and generalization items. Power estimates were binned into four frequency bands (theta, alpha, beta, gamma). (A) Averaged oscillatory power (log-transformed) of old and generalization trials in the transfer phase in the 2 – 45 Hz spectrum. While theta power was significantly increased, the remaining frequency bands showed a significant decrease during the transfer phase. (B) Average oscillatory power (log-transformed) for both old and generalization trials of the transfer phase. No differences in oscillatory power between old and generalization trials were found in either of the frequency bands.

investigate the temporal and spatial pattern-similarity of theta activity during generalization trials compared to old trials. Results from the RSA *across* stimulus categories were averaged over trials and contrasted to 0 using an independent sample cluster-based permutation t-tests. This analysis allowed us to test when and where theta activity was significantly (dis-)similar during the processing of generalization and old trials.

As evidence suggests a potential dependence of memory generalization from neural activity of the acquisition of information (Sans-Dublanc et al., 2017), we repeated parts of the previous analyses. We again applied an oscillatory power analysis to read out overall theta activity during new trials of the *acquisition* phase. Theta activity was then correlated (Pearson) with the generalization performance of the *transfer* phase. We next handed time–frequency representations of old and new trials from the *acquisition* phase to a dependent sample cluster-based permutation *t*-test. Lastly, we repeated the *within*-category RSA for old and new trials of the *acquisition* phase, yet only for the theta frequency band.

Data analyses were performed with R version 3.3.6 (Dessau & Pipper, 2008) as well as Matlab (The MathWorks). All reported *p*-values are two-tailed and Greenhouse-Geisser correction was applied if required. Outliers were identified and excluded when exceeding ± 3 absolute deviations from the median (Leys et al., 2013). Data as well as scripts related to the analyses (R, MatLab), are available upon request).

## 3. Results

### 3.1. Behavioral Results

Overall, participants learned the antecedent-consequent stimulus-pairs very well, as reflected in an average performance of about 85 % in the acquisition phase (Fig. 1A, right column). A one-way ANOVA showed a main effect of the factor *stage* ($F_{(2,104)} = 9.41$, $p < .001$, $\eta^2 p = .153$), indicating an increase of performance across stages, which may be due to familiarization with the task procedure and the fact that each stage included trials from the previous ones. Performance for new trials was significantly above chance level during the stages *equivalence learning* ($t_{(52)} = 28.84$, $p < .001$, $d = 3.96$) and *new consequents* ($t_{(54)} = 28.18$, $p < .001$, $d = 3.80$), suggesting that participants were capable of linking the previously acquired and newly presented information.

In the critical *transfer phase,* that provided a test of memory generalization, memory performance for old stimulus-pairs was very high (90.72 ± 5.77) and significantly higher than for generalization stimulus-pairs (75.07 ± 17.83; $t_{(52)} = 8.96$, $p < .001$, $d = 1.62$; Fig. 1B, right column). Performance for generalization stimuli, however, was significantly above chance level ($t_{(52)} = 10.23$, $p < .001$, $d = 1.41$), indicating

overall successful memory generalization.

### 3.1.1. Explorative analysis of gender differences

We ran an explorative analysis testing for potential differences in memory generalization performance between men and women. However, neither during the acquisition phase, nor in the transfer phase, we obtained any reliable performance differences between men and women (all interactions and main effects including *gender*: all $F < 2.24$, all $p$'s >

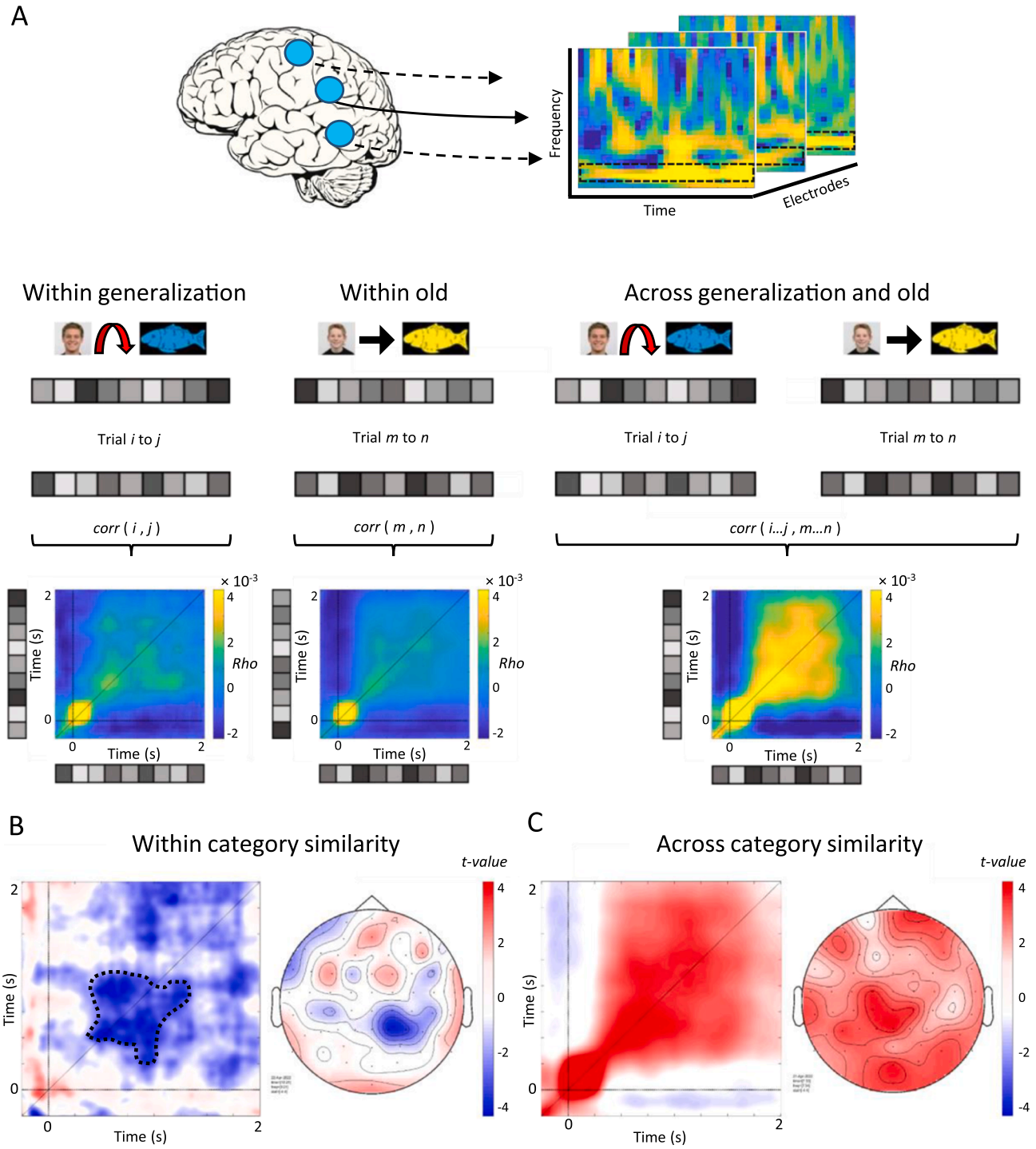


**Fig. 3.** Increased representational dissimilarity in right centro-parietal area during memory generalization compared to pure memory retrieval. (A) Representational Similarity Analysis on sensor level frequency data. Following pre-processing, trial-wise time–frequency representations (TFRs) were calculated. Next, TFRs were correlated electrode-wise, trial-wise and across all time points using Spearmans' correlations. We first calculated the within-category similarity for old and generalization trials separately and compared these similarities using a cluster-based *t*-test. Additionally, trials from both categories were correlated with one another in order to estimate the similarity across both categories. (B) Results from the cluster based permutation *t*-test comparing within- category similarity maps of old and generalization trials. The *t*-map and corresponding topography plot represent the average similarity of sensors *P4* and *P6*, forming a significant cluster marked by the dashed area. (C) Results from the cluster based permutation *t*-test comparing the across-category similarity against 0. The *t*-map and corresponding topography plot represent the average similarity of all sensors. The *t*-map and corresponding topography plot show the significant positive widespread cluster of theta activity similarity across both categories of all sensors.

0.124, all $\eta^2$p <.420).

### 3.2. Oscillatory power analysis

We hypothesized that theta oscillations would be particularly relevant for successful memory generalization given the known role of theta in associative memory processes (Clouter et al., 2017). In order to probe the relevance of theta oscillations for memory generalization, we first quantified the oscillatory power during all trials of the transfer phase of our experiment (from 0 to 2 s, relative to stimulus onset). Visual inspection of the frequency spectrum indicated the expected dominance of theta power oscillations (Fig. 2A). For statistical validation, power estimates were binned in four bands (theta [4 – 7 Hz], alpha [8 – 12 Hz], beta [13 – 30 Hz], gamma [31 – 45 Hz]). A one-way ANOVA including the factor *frequency band* revealed that theta activity was overall increased compared to other frequency bands (main effect *frequency band*: $F_{(1,84)} = 84.38$, $p$ <.001, $\eta^2$p =.605; Fig. 2B). Post-hoc tukey tests indicated significantly stronger theta oscillations compared to all other frequency bands over the averaged trial length (all $t > 7.835$, all $p$'s$_{corr}$ < 0.001). An ANOVA including the factors *frequency band* and stimulus *category* (old vs new) indicated, however, that oscillatory power did not differ between generalization and old items (interaction *frequency band* × *category*: $F_{(3,440)} = 0.04$, $p$ =.989, $\eta^2$p =.002), which may be due to the fact that both stimulus categories originate from an associative learning context, in which theta activity plays a central role.

### 3.3. Memory generalization is accompanied by theta band pattern dissimilarity

As our oscillatory power analysis pointed to a particular relevance of theta oscillations in the context of associative learning (Fig. 2), we next contrasted time–frequency representations associated with old and generalization stimulus-pairs from the *transfer phase* on sensor level. The cluster-based permutation *t*-test did not reveal a significant difference between both stimulus categories ($p$ =.435; ci-range = 0.009; SD = 0.005), indicating no overall theta power differences between old and generalization stimulus-pairs, which further supports the idea that not the amplitude of theta power per se is linked to memory generalization.

Next, we focussed on the key question of our study, whether memory generalization is linked to stimulus-specific patterns of theta activity. We therefore utilized a RSA *within* old and generalization stimulus-pairs separately (Fig. 3A), estimating similarity in theta activity between all possible pairs of stimuli. The resulting similarity maps of both categories (41 time points × 41 time points × 64 electrodes) were entered into a dependent sample cluster-based permutation *t*-test, which revealed a significant negative cluster during generalization stimulus-pairs compared to old stimulus-pairs ($p$ =.012; ci-range = 0.002; SD = 0.001), indicating increased spatio-temporal theta pattern dissimilarity during memory generalization compared to memory retrieval. This pattern dissimilarity was localized on electrodes *P*4 and *P*6, covering the right right centro-parietal area, from 0.4 to 1.1 s relative to stimulus onset (Fig. 3B). In order to rule out that the observed pattern dissimilarity was rooted in an oscillatory power difference between trial-categories (old, generalization) in the given time-window, we calculated the oscillatory theta power between 0.4 and 1.1 s relative to stimulus onset and compared them between stimulus categories using a dependent sample cluster-based permutation *t*-test. This test did not yield a significant difference of activity (all p >.324; see supplemental Fig. 1). Thus we can rule out mean amplitude differences of both stimulus categories, potentially being responsible for the observed difference in RSA patterns in the transfer phase. Utilizing the identified time window and location, we next correlated generalization performance with theta band dissimilarity (averaged from 0.4 to 1.1 s to stimulus onset as well as averaged over electrodes *P*4 and *P*6). The Pearson correlation did not reveal a significant relation of generalization performance and theta band dissimilarity ($r$ = 0.030, $p$ =.820).

Finally, we used a RSA to compare old and generalization stimulus-pairs *across* categories in order to investigate the neural similarity between these stimulus categories. The resulting similarity maps were tested against 0, using an independent samples cluster based permutation *t*-test, and revealed a significant positive widespread cluster of theta activity similarity *across* both categories ($p$ <.001; ci-range < 0.001; SD < 0.001), indicating that old and generalization stimulus-pairs were processed with an overall similar pattern of theta activity, which was expected as both categories reflect activity from an associative learning context (Fig. 3C).

#### 3.3.1. Explorative analysis of other frequency bands

Although our previous analyses pointed to a specific role of theta in associative learning, we extended the time–frequency analyses also to alpha, beta, and gamma, in order to test the distinct role of theta oscillations in memory generalization. Dependent samples cluster permutation t-tests did not reveal any significant cluster in any of the three other frequency bands (all $p$'s > 0.138).

We also ran an explorative analysis of the RSA data using the *within* and *across* category approach, but this time extracted feature vectors from the remaining three frequency bands (alpha, beta, gamma). This way we probed whether there are similar representational patterns linked to memory generalization in other frequency bands than theta. Comparisons of *within* phase similarity did not reveal any significant differences in either of the remaining three frequency bands (all $p$'s > 0.317), suggesting a distinct role of theta oscillations during memory generalization.

Similarity analyses *across* stimulus categories revealed positive clusters in the alpha ($p$ <.001; ci-range < 0.001; SD = < 0.001), beta ($p$ <.001; ci-range < 0.001; SD = < 0.001) and gamma band ($p$ <.001; ci-range < 0.001; SD = < 0.001), suggesting that generalization and old trials were overall processed with the same specific patterns of oscillatory activity. This is not surprising because information of old and generalization trials are strongly overlapping as they are derived from the same integrative (associative) encoding task and may reflect basic task-related neural activity (i.e., attention and visual activity) that does not differ between stimulus categories.

### 3.4. Theta band analyses during the acquisition of associative memories

As previous evidence suggested a potential role of theta activity during the formation of associative memories and later generalization (Sans-Dublanc et al., 2017), we repeated the oscillatory power as well as time–frequency and RSA (*within*-category) analyses, yet this time focussing on stimulus-pairs from the acquisition phase. This analysis was thus directed at the integrative encoding account of memory generalization, which assumes that overlapping information is represented in a mnemonic network that enables the flexible retrieval required for generalization (Shohamy & Wagner, 2008). Results showed no significant correlation between overall theta power during new trials of the acquisition phase with the generalization performance during the transfer phase ($r$ = -0.040, $p$ =.769). Time-frequency analyses between representations associated with old and new stimulus-pairs were next subjected to a cluster-based permutation *t*-test. Results did not reveal a significant difference between both stimulus categories (all $p$'s > 0.398), indicating no overall theta power differences between old and new stimulus-pairs during their acquisition. Similarity analyses *within* stimulus categories also revealed no significant difference of *within*-category similarity between old and new trials during the acquisition phase (all $p$'s > 0.092).

## 4. Discussion

Episodic memories enable us not only to remember events from the past but provide also guidance for similar future situations. Although the generalization of information from the past into a current context is a

fundamental memory process (Pedraza et al., 2022; Herszage & Censor, 2018; Ghosh & Chattarji, 2015), the neural mechanisms underlying the transfer of information across episodes are not yet fully understood. In particular, the spatio-temporal patterns associated with memory generalization remain elusive. In the current study we used EEG, with its excellent temporal resolution, to study the role of theta oscillations during associative memory generalization compared to mere memory retrieval. In an acquired equivalence paradigm, our behavioural results showed that participants were able to acquire and later generalize information across episodes. Our time–frequency and RSA data revealed an overall high similarity during memory generalization and retrieval. Importantly, however, theta patterns in the right centro-parietal area were significantly more dissimilar during generalization compared to retrieval, suggesting a specific neural signature of memory generalization. Although it remains unclear whether these differences were due to qualitative differences between generalization and retrieval or different demands associated with these processes (or both). No such differences were observed in the alpha, beta, or gamma band, pointing to a potentially specific role of theta in memory generalization. Notably, theta oscillations during acquisition trials were not linked to memory generalization.

Theta oscillations are thought to be a central component of associative memory, acting as a driving force of hippocampal neuronal plasticity (Jutras et al., 2013; Huerta & Lisman, 1995). Theta activity is suggested to integrate and therefore bind information of episodic memories together through transient interactions across brain regions, forming an oscillatory mechanism underlying memory formation and retrieval (Hanslmayr & Staudigl, 2014; Buzsáki & Moser, 2013; Nyhus & Curran, 2010)). We therefore reasoned that the generalization of associative memories would be processed with an association-specific pattern of theta activity compared to retrieval trials. Results of our *within*-category RSA revealed that during memory generalization, trials were indeed processed with a dissimilar pattern of theta activity, localized in the right right centro-parietal area, compared to memory retrieval. This dissimilarity among neural patterns is not only temporally fine-grained but can also be attributed to a specific location and frequency. This is supported by the fact that we did not observe a comparable effect in any of the remaining frequency bands (alpha, beta, gamma). It may therefore reflect the neural fingerprint of the individual components of distinct associative memories being transferred and bound together to form a new, generalized, association relying on specific (and therefore unequal) patterns of theta activity. Importantly, this dissimilarity in theta patters was also not observed during the acquisition of information, which might be predicted based on an integrative encoding account, which assumes that the formation of overlapping memory representations during encoding is essential for subsequent generalization (Zeithamova & Preston, 2010; Shohamy & Wagner, 2008). The absence of an effect during acquisition could be interpreted as support for the view that memory generalization is based on a flexible expression of associative components during retrieval (Eichenbaum, 2000; Cohen & Eichenbaum, 1995).

Importantly, the observed dissimilarity in theta pattern activity during generalization was observed specifically in the right centro-parietal area, covering the parietal lobe. Activations of the parietal lobe have been previously linked to working memory processes (for a review see Wager & Smith, 2003), the maintenance of information (Rowe et al., 2000) but also attentional demands (Berryhill & Olson, 2008; LaBar et al., 1999). Lesion data further suggest that especially the superior parietal lobe is associated with deficits involving the manipulation and reorganization of information in working memory, but not in working memory tests requiring only retrieval processes (Koenigs et al., 2009). This reorganization of information is also highly relevant in memory generalization, as new associations have to be formed after recalling elements of known episodes. It has been demonstrated that posterior theta connectivity increases with the executive demand during working memory (Sauseng et al., 2005). This finding also dovetails with our finding in the right centro-parietal area, as during the transfer phase participants were either required to simply retrieve (low-executive demand) an event or reactivate two separate events to build a new association via generalization (high-executive demand).

Results from our oscillatory power analysis indicated a significant increase of overall theta activity during memory generalization. The follow-up time–frequency analysis comparing generalization and retrieval trials revealed no significant difference of theta power at any location, indicating that it is not theta power per se which is associated with memory generalization. Most likely, this absence of such a difference reflects the overall similar processing of generalization and retrieval trials. Although both trial categories included different stimulus combinations, the presented information yielded a high amount of overlap. Hence, we assume that the overall increase in theta power during generalization and retrieval may partly be rooted in equal processing in relevant cognitive domains, such as visual processing or attention and for both retrieval and generalisation.

Although our behavioural data show a significant difference in performance between retrieval and generalization trials, time–frequency analyses did not reveal a significant difference in theta power at any location, posing a potential limitation to our findings. It is however worth noting that time–frequency analyses (which rely solely on oscillatory power) do not capture every characteristic of neuronal oscillations. In order to capture the activity patterns (and their similarity) over time, we used here an RSA approach, which has not been reported so far in the context of memory generalization. Future studies are required to replicate our findings using a similar approach. Furthermore, we did not obtain an association between generalization performance and dissimilarity of the significant RSA cluster. The absence of such a correlation might indicate that theta dissimilarity does not reflect the degree of generalization performance but rather the process of memory generalization, irrespective of its success. Moreover, the absence of a brain-behaviour correlation might be due to the performance level in the task: many participants showed excellent, near ceiling generalization performance, which may have obscured an association. Future studies should use task variants including, for example, more associations between stimuli in order to achieve a higher variability in task performance, which may provide a better basis for tests of brain-behavior associations. Moreover, future studies could include separate tasks to assess more general cognitive processes, such as logical reasoning, which – unlike memory generalization – do not have a major memory component but are inherently involved in memory generalization. Such additional tasks would allow probing the specificity of the current observations to memory generalization. Such additional tasks would allow probing the specificity of the current observations to memory generalization. In sum, our data provide novel insights into the neural underpinnings of memory generalization. Specifically, we show that the generalization across past events is linked to distinct and therefore dissimilar patterns of theta activity in the right centro-parietal area. Importantly, this effect was not during acquisition or mere retrieval. The generalization-related change appeared further to be specific to theta oscillations. The present findings suggest that distinct patterns of theta oscillations are involved in the flexible recall and binding of elements across separate episodes to form new associations in an area well known for its role in (working) memory processes. Through their role in memory generalization, theta oscillations contribute to adaptive memory processes that leverage past events to guide future behaviour.

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## CRediT authorship contribution statement

**Hendrik Heinbockel:** Formal analysis, Methodology, Visualization, Writing – original draft. **Conny W.E.M. Quaedflieg:** Conceptualization, Project administration, Data curation, Writing – review & editing. **Jan Wacker:** Resources, Validation, Writing – review & editing. **Lars Schwabe:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2022.105926.

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