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The roles of EEG oscillations in learning relational information

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Rhythmic brain activity has been implicated in learning and memory. Many models implicate theta oscillations (4–8 Hz) specifically in learning of relational information such as pairings and ordered lists. We tested this hypothesis in humans by recording electroencephalographic activity while participants studied nouns organised into pairs or triples for a later cued recall test. If theta is critical in learning structured information, then the amount of theta activity present during study of pairs and triples should covary with subsequent memory performance (accuracy and response times). Multivariate partial least squares analysis revealed three patterns of oscillatory activity associated with task conditions in different ways: a) Within subjects, successful study of pairs but not triples was associated with elevations in oscillations at multiple frequencies including theta, b) Frontal theta oscillations, in conjunction with beta oscillations, covaried with memory performance across subjects for both pairs and triples and c) Right-lateralized gamma oscillations in conjunction with low-frequency oscillations were associated with faster responding at the expense of accuracy across subjects for both pairs and triples. These findings support models that implicate theta oscillations in learning structured information rather than item information alone but similar to prior reports, suggest that theta oscillations explain individual variability better than trial-to-trial variability in behavior. Crown Copyright © 2007 Published by Elsevier Inc. All rights reserved.

Introduction

Theta oscillations are rhythmic-wave activity observed in the electroencephalogram (EEG) in many experimental settings (Jung and Kormmüller, 1938). The theta rhythm has been implicated in learning and memory function both in humans (e.g., Burgess and Gruzelier, 1997; Doppelmayr et al., 2000; Guderian and Düzel, 2005; Jensen and Tesche, 2002; Klimesch et al., 1996, 1997; Sederberg et al., 2003) and other animals (e.g., Adey et al., 1960, 1962; Berry and Thompson, 1978; Givens, 1996; Griffin et al., 2004; Lee et al., 2005; O'Keefe and Recce, 1993). Memory psychologists have long drawn a significant theoretical distinction

among memory for a) individual items, b) associations (pairings) between items and c) ordered sequences of items (Murdock, 1970). Some models of the theta implicate this oscillation specifically in learning of relational rather than simple item information—namely, the timing of the activations of neural representations within the theta cycle (i.e., phase information) preserves information about their pairings and ordering (e.g., Borisyuk and Hoppensteadt, 1998; Fukai, 1999; Jensen and Lisman, 2005), a notion first put forward by McLardy (1959) and then Adey et al. (1962). For many of studies reporting study-related theta, the theta activity could relate to relational rather than single-item learning. However, these studies have only directly tested memory for single items. Our chief objective was to test whether theta oscillations would be specifically invoked during successful study of associative and sequence information by analyzing EEG activity during study of word pairs and triples.

Whereas hippocampal theta oscillations dominate the rat EEG (e.g., Bland, 1986), it is more controversial whether the normal adult human waking EEG contains theta oscillations as a distinct physiological phenomenon (Niedermeyer, 1999). If theta rhythms occur in human scalp-recorded EEG, they may be difficult to make out by visual inspection amid the background signal, or they may occur during specific cognitive events that are rare enough that they may appear to be Type I error. The existing literature is inconclusive on this question. Studies of theta have typically been based on planned comparisons that focus exclusively on the theta band making it impossible to test for frequency-band specificity. Multivariate analysis encompassing a broad frequency band attempts to best characterize the distributed pattern of oscillatory activity, grouping together oscillations at various frequencies and locations when they share a common covariance structure. If the results group together theta-band activity separately from activity at other frequencies, this would confirm the validity of the theta band as a distinct construct. If theta-band activity were always grouped with activity over a broad band of neighbouring frequencies, this would suggest that the theta band is simply a narrow window into a more complex neural signature.

Several studies have taken this latter approach (Düzel et al., 2003, 2005a, 2005b), applying a partial least-squares (PLS) analysis to EEG and magnetoencephalographic (MEG) activity. PLS identifies distributed patterns of brain activity (or correlation

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with extrinsic measures) that bear a specific relationship to the task design (i.e., contrasting or relating task conditions with one another). Each of these brain–behavior relationships, or latent variables, implicated some activity within the theta band but also activity at other frequencies. Most notably, a latent variable showing a subsequent memory effect (SME; difference between study activity for later recalled vs. later not-recalled information) for a subsequent verbal priming test involved increases in theta-band activity associated with priming along with decreases in beta-band activity (Düzel et al., 2005a,b). Thus, for the priming-SME, the theta band may represent a distinct type of activity but this is coupled with concurrent decreases in beta activity. Using independent components analysis, Onton et al. (2005) identified a pattern of theta-band power combined with beta-band power that increased with memory load during a single-item recognition memory task, suggesting that theta activity may be coupled to beta activity.

We investigated broadband oscillatory activity while participants studied for a subsequent explicit test of relational memory (pairs and short lists). In cued recall, one can probe in the forward or the backward direction. For example, a pair, A–B may be probed forward by giving the first item as a cue and asking for the second one (A–?) or backward (?–B). Forward and backward probes of pairs and triples yield nearly the same accuracy and response time, and moreover, are also nearly perfectly correlated (Kahana, 2002; Caplan et al., 2006). That is, if a participant can answer the forward probe accurately they can almost certainly answer correctly to the backward probe. Further, pairs are recalled more accurately and faster than triples, and triples probed for the first portion of the triple (probes A–? or ?–B) are recalled more accurately and faster than triples probed for the second portion of the triple (B–? or ?–C). What makes the triples more difficult than the pairs appears to be interference from the additional item in the triple that needs to be ruled out (Caplan et al., 2006). In previous time-domain analysis of EEG activity during study of pairs and triples we found that three classic event-related potential (ERP) components that have exhibited SMEs for tests of single-item memory also showed SMEs for tests of associations and order (Caplan et al., submitted), including an early potential (~200 ms after stimulus onset), a late positive component (~550 ms) over posterior sites and slow potentials involving left frontal and occipital topographies. Here we analyze the same data set in the frequency domain and ask whether oscillations in a broad frequency range (2–38 Hz) relate to effective study of pairs, triples or both.

Materials and methods

The experimental methods are identical to those described previously (Caplan et al., submitted for publication).

Participants

26 healthy adult volunteers whose primary language was English participated for monetary compensation (10 male, 16 female, 1 left-handed, age=29.7±9.4 years). Six participants were excluded due to ceiling (percent correct>90%) or floor (percent correct<10%) performance in at least one condition (pairs/AB-Triples/BC-Triples; see Materials), leaving 20 included participants (9 male, 11 female, 1 left-handed, age=27.6±7.7 years).

Behavioral methodology

Materials

The fixation (apart from those preceding a pair or a triple) consisted of seven asterisks presented in the center of the screen, displayed for 3750 ms and then erased for 250 ms.

The lists consisted of nouns from the Toronto Word Pool (Friendly et al., 1982), randomly sampled without replacement. Each noun was presented visually in the center of the screen. The lists were grouped either into 9 pairs or into 6 triples, which kept the total list-length at a constant 18 words. The order of pair lists and triple lists was chosen randomly, with the constraint that each set of three lists had to include one pair list and two triple lists. Each noun was displayed for 1750 ms, followed by 250 ms blank inter-stimulus interval (ISI). An additional interval of 4000 ms was inserted between pairs and triples. During this inter-block-interval, the participant viewed strings composed of a single digit enclosed by three asterisks on either side: ***2*** (lists of pairs) or ***3*** (lists of triples). This inter-block cue served to remind the participant of whether they were studying a list of pairs or triples.

The distractor consisted of 4 equations of the form $A+B+C=?$, where A, B and C were randomly selected digits from 0 to 6, with the restriction that the identical distractor could not be used twice in succession. The equation remained on the screen for 3750 ms and then was erased for 250 ms. The participant was asked to respond vocally with the correct answer to the equation within the entire 4000 ms interval given.

Cued recall consisted of a word with six question marks, ?????? either to the left or to the right of the probe word. The participant was instructed to recall the word that followed or preceded the probe item depending on whether the question marks were placed to the right or left of the probe word, respectively. Each probe was preceded by a fixation. The probe remained on the screen for 7000 ms and then was erased for 1000 ms. The participant was asked to respond vocally within the entire 8000 ms interval given. Each pair and triple was probed exactly once, and probe order was selected at random. Triples could be probed for the first portion of the triple (A? or ?B) or for the last portion of the triple (B? or ?C). Triples probed in each way will be referred to as “AB-Triples” and “BC-Triples,” respectively.

Procedure

Fig. 1 illustrates the procedure for a single trial. Participants first viewed a fixation. Then, they studied the list in a single study trial. Next, they performed the distractor task and finally, they answered cued recall questions based on the list. A session consisted of 26 lists.

For the first list, self-paced instructions preceded each of the study, distractor and cued recall phases of the task. During the instruction periods, the experimenter ensured that the participants understood the instructions. The first two lists included one pure list of pairs and one pure list of triples; the order of these was randomized across participants. These first two lists were considered practice and are excluded from all analyses.

EEG methodology

EEG signal was recorded from a 64-electrode cap (Electro-Cap International), including the sites Fp1, Fp2, F4, F3, C3, C4, P4, P3, O2, O1, F8, F7, T4, T3, P8, P7, Pz, Fz, Cb1, Cb2, TP7, TP8, Oz, Iz, PO4, PO3, CP5, CP6, CP1, CP2, FT9, FT10, FC2, FC1, AF3, AF4,

a A list of pairs									
Study	AB	CD	EF	GH	IJ	KL	MN	OP	QR
	████████████████████								
Distractor									
Test 1	O?	M?	?H	?R	C?	A?			
Test 2	?D	O?	?R	?N	A?	G?			

b A list of triples						
Study	ABC	DEF	GHI	JKL	MNO	PQR
	████████████████████					
Distractor						
Test 1	E?	?B	Q?	?H	?K	N?
Test 2	?K	N?	A?	E?	G?	?R

Fig. 1. Behavioral procedure. (a) A single pair-list trial. Each capitalized letter represents a unique noun. In a study trial, words are presented grouped in pairs. A mathematical distractor follows (denoted by the grey rectangle), and then a set of cued recall probes of the list. Six of the nine pairs; the remaining three pairs are not probed at all. (b) Procedure for a single triple-list trial. All triples are probed.

FC6, FC5, CPz, P1, POz, P2, P6, C6, P5, C1, C2, C5, F2, F6, F1, AF8, F5, AF7, Fpz, and FCz (American Electroencephalographic Society, 1991). Electrodes were also placed on the left and right mastoids (TP9, TP10), on the left and right zygomatic arch (F9, F10), at the outer canthus of the each eye (LO1, LO2), and on the infraorbital ridges directly below each eye (IO1, IO2). An electrode at AFz was used as ground and an electrode at Cz was used as reference. Inter-electrode impedances measured at 10 Hz were below 5 k Ω . EEG and EOG signals were amplified with Neuroscan SynAmps at a gain of 2500 with an online analogue filter bandpass of 0.05–100 Hz (–3 dB points; 12 dB/octave). Data were recorded at 500 Hz. EOG compensation was applied using ocular source components (Berg and Scherg, 1991; Picton et al., 2000). A separate ocular calibration recording was obtained during which participants blinked and made saccades in the up, down, right, and left directions. Five saccades in each of the four directions and 10 blinks were averaged. An ocular data set was assembled by concatenating average recordings of each of the saccades and the blinks for each participant individually. A principal component analysis of these data for each participant provided a set of components that represented the variance related to the eye movements. Three components, each explaining more than 1% of the variance and each specifically related to the EOG waveforms were used as source components to subtract EOG contamination from the recorded EEG. The signal was then converted to an average-reference montage with 65 channels. Traces were notch-filtered at 60 Hz to remove line noise. Trials with voltage deviating more than 300 μ V from baseline were excluded from all analyses.

Oscillatory episode detection method

To measure levels of oscillations we wanted a method that would be conservative about identifying EEG activity as oscillatory and to exclude non-rhythmic signal (which can

nonetheless produce increases in power at a given frequency). To this end, we used the method introduced by Caplan et al. (2001). This method identifies epochs of EEG signal with high power at a particular frequency lasting several cycles. The method excludes much of the background noise by estimating the noise spectrum. A minimum-duration threshold helps to exclude evoked potentials as well as non-rhythmic artifacts. The analysis is performed separately at each frequency of interest and each electrode. For a given frequency, f^* , an oscillatory episode is defined as an epoch longer than a duration threshold, D_T (in numbers of cycles) during which wavelet power at frequency f^* exceeded a power threshold, P_T . The two threshold parameters were chosen as follows: (1) We wavelet-transformed the EEG in the entire set of trials to be analyzed (Morlet wavelet, window=6 cycles; Grossmann and Morlet, 1985) at 22 logarithmically spaced frequencies in the range 1–54 Hz. The average of the log-transform of these wavelet values yielded the wavelet power spectrum. Note that in contrast to prior applications of this method we log-transform before averaging rather than after; this reduces sensitivity to extreme values likely due to noise or artifacts. This modification was introduced by van Vugt et al. (2007). (2) We assumed that the background noise spectrum has the form $\text{Power}(f) = Af^{-\alpha}$. We estimated this background by fitting the observed spectrum (at each electrode) with a linear regression in log–log units. Because wavelet power values are expected to be distributed like $\chi^2(2)$ (Percival and Walden, 1993), the estimated background at f^* should be the mean of its corresponding $\chi^2(2)$ probability distribution function (PDF). We chose $P_T(f^*)$ to be the 95th percentile of the fit PDF. Power thresholding should exclude about 95% of the estimated background signal. (3) We set D_T to three cycles of f^* , or $D_T(f^*) = 3/f^*$. This was done to eliminate artifacts and nonrhythmic physiological signals. (4) Finally, $P_{\text{episode}}(f^*)$, or the proportion of time in oscillatory episodes, was defined as the total amount of trial time filled with detected oscillatory episodes divided by the total time in the trial (namely, 2 s). In subsequent analyses, we considered the 2–38 Hz range, excluding frequencies at the ends of the spectrum to keep clear of the bandpass filtering of the amplifiers (high-pass) and the skull and scalp (low-pass). These $P_{\text{episode}}(f)$ values at each electrode were averaged across trials within participants and then analyses were performed across participants. For the purposes of interpretation of the results, the following frequency band conventions are used. Delta: <4 Hz, Theta: 4–8 Hz, Alpha: 9–12 Hz, Beta: 13–30 Hz, Gamma: >30 Hz.

Note that the oscillatory episode detection algorithm applied here evaluates rhythmic activity against what would be expected based on an estimated of the background “noise” signal. Thus, we can state that the levels of oscillatory activity reported here exceed what would be expected given the null hypothesis that the EEG contains only background signal. We do not know whether the observed levels of oscillations are increases or decreases over a “baseline” cognitive state. We can, however, make informative statements comparing oscillatory activity between conditions and correlations of oscillatory activity with individual differences in behavior. For this reason, throughout the manuscript we only use the terms “increase” and “decrease” in their relative sense.

Partial least-squares analyses

Overview

The motivation of this analysis was to identify distributed patterns of oscillatory activity and characterize their relationship to

task conditions (pair vs. triple and recalled vs. not recalled) and to individual differences in behavior (overall accuracy and correct-response response time (RT) were used as behavioral covariates). Multivariate methods can concisely summarize these effects and allow us to ask questions regarding similarity and difference of brain activity patterns without biasing the analysis based on preconceptions about which components will be most relevant. PLS is a multivariate technique that describes the relationship between the input, e.g., task design, and output measures, e.g., brain activity or brain activity–behavior correlations as a function of condition (McIntosh et al., 1996, 2004; McIntosh and Lobaugh, 2004). A Task PLS analyzes mean changes in brain activity as a function of conditions to assess overall presence or absence of distributed patterns of brain activity in each condition (the within-subjects approach). In a complementary approach, Behavior PLS analyzes the correlation between brain activity and behavioral covariates (e.g., accuracy or response time) to identify distributed patterns of brain activity that have relevance to behavior across participants (the between-subjects approach). The combination of the Task and Behavior PLS enables us to identify distributed patterns of oscillatory activity that account for both within-subjects variability across conditions (Task PLS) and between-subjects variability as a function of condition (Behavior PLS).

PLS input

Task PLS (within-subjects approach). To compare pairs versus triples and to look for the SME, we had four conditions: PAIR/TRIPLE[2]×MEMORY[2]. For each condition, activity consisted of P_{episode} as a function of frequency (2–38 Hz band) and electrode. Each row represents a different condition and columns represent electrode×frequency, the values consisting of the corresponding P_{episode} values. Thus, the Task PLS input matrix has size 4 rows (conditions) and 1220 columns (61 electrodes×20 frequency samples). The columns of the Task PLS matrix are mean centered.

Behavior PLS (between-subjects approach). Two submatrices were created, one for Accuracy and one for RT. The input to the Behavior PLS is the columnwise concatenation of the Accuracy and RT submatrices. Each submatrix is normalized separately. The P_{episode} values at each electrode and frequency were correlated with accuracy or RT, respectively, across participants. Note that accuracy for pairs referred to overall accuracy for pairs, thus the same accuracy values were correlated with activity during study of subsequently recalled pairs and subsequently not recalled pairs. The same applies to triples, as well as to RTs for pairs and triples, respectively. Each row represents a different condition and columns represent electrode×frequency, the value consisting of the correlation between P_{episode} and either accuracy or RT across participants. Thus, each of the two Behavior PLS submatrices (one for accuracy and one for RT) has the same dimensions as the Task PLS input matrix.

PLS procedure

A singular value decomposition (SVD) is applied to the input matrix to compute an optimal *least-squares* fit. This produces a set of mutually orthogonal latent variables (LVs), each consisting of two parts: a singular image (“brain LV”, or the brain portion of the latent variable) and a singular profile (“design LV” or “behavior LV”, or the design/behavior portion of the latent variable), connected by a singular value (the square root of the eigenvalue). The singular value indicates how much of the covariance of the input matrix is accounted for by its respective latent variable. Brain

LVs consist of a weighted linear combination of electrode/frequencies that as a whole covary with each behavioral covariate’s value across participants. The numerical weights within the brain LV are called “salience” and can be positive or negative, indicating the degree to which each electrode/frequency is related to the design/behavior LV. For Task PLS, the design LV reveals how the brain LV varies across conditions, analogous to a contrast. For Behavior PLS, the behavior LV reveals the nature of the brain–behavior covariance, and in particular, how this covariance varies across task conditions. The behavior LV thus tells us whether/how the brain LV accounts for individual variability in performance.

Assessing reliability

The significance of each LV is assessed with a permutation test (2500 iterations) in which task condition labels are shuffled. This results in a distribution of singular values from shuffled data sets, from which the cumulative 95th percentile is taken as the significance threshold. The reliability of the contribution of each electrode/frequency to the LV is assessed by a bootstrap estimation of standard errors for the salience (500 iterations) by resampling participants. Salience whose 95% confidence intervals (based on the standard error) do not include zero are considered reliable across participants; reliable electrode/frequencies are denoted in brain LV figures with an asterisk. We also use the results of the bootstrap to similarly compute 95% confidence intervals on correlations between the brain LV and the behavioral measures. The brain LV can be projected onto each participant’s P_{episode} (electrode, frequency) pattern as a function of condition to obtain scalp scores (analogous to factor scores in a factor analysis), to assess how consistent each individual participant’s activity is with the brain LV derived from the population analysis. Confidence intervals for mean scalp scores are computed over scalp scores for each participant, corrected for between-subjects variance following Loftus and Masson (1994).

Results

To investigate the brain–task and brain–behavior relationship we ran two partial least squares (PLS) analyses, a Task PLS and a Behavior PLS. PLS breaks down either brain activity as a function of condition (Task PLS; within-subjects approach) or the correlation between brain activity and relevant behavioral measures (i.e., accuracy and response time) as a function of condition (Behavior PLS; between-subjects approach). The method is similar to factor analysis or PCA in that patterns of brain activity will emerge from the analysis, but critically, it constrains the solution to relate to the task design, striking a balance between hypothesis-testing and exploratory analysis. Task PLS contrasts conditions within subjects, whereas Behavior PLS explains how brain activity covaries with individual variability in performance. The combination of the two analyses gives us a more complete picture of brain activity related to successful study processes.

Task PLS (within-subjects approach)

Task PLS explains differences in mean activity levels across conditions within participants. This analysis identified one significant latent variable (LV), accounting for 52% of the cross-block covariance (Fig. 2). The design LV (panel a) tells us whether the identified activity pattern differed across conditions in overall activity; this corresponds to a within-subjects contrast. This LV

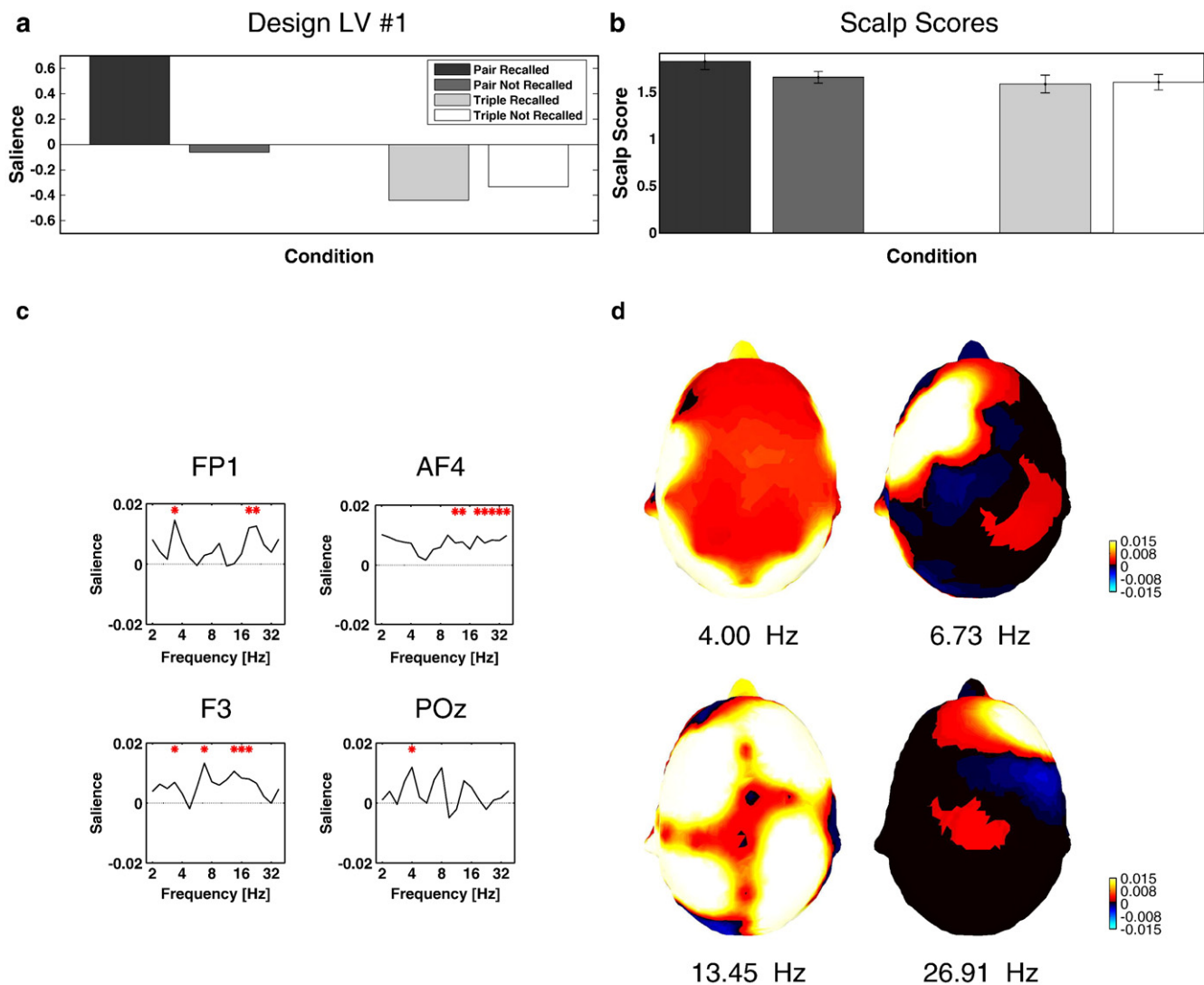


Fig. 2. Task PLS (within-subjects approach), Latent Variable #1. (a) Design LV, salience is plotted as a function of condition, characterizing how the brain LV pattern varies on average as a function of condition. (b) Scalp scores, the projection of the brain LV onto each condition. Error bars plot 95% confidence intervals across participants, corrected for between-subjects variability. (c) Brain Latent Variable #1 at sample electrodes as a function of frequency. Red asterisks denote frequencies for which the salience was reliable (bootstrap ratio > 1.96, equivalent to z scores with a *p* value of 0.05). (d) Topographic spline maps plotting salience across the scalp at sample frequencies, wherever the bootstrap ratio magnitude exceeded a threshold of 1.96 (unreliable saliences are plotted in black). Color scale denotes bootstrap ratio.

contrasted study activity for subsequently recalled pairs compared to subsequently not-recalled pairs and to triples regardless of subsequent memory. To complement the design LV, the scalp scores (projection of the brain LV onto each subject's average) tell us the absolute levels of the brain LV. Panel b plots the mean scalp scores as a function of condition and 95% confidence intervals across subjects. By comparing confidence intervals we find that this LV is reliably contrasting recalled pairs from the other three conditions, although all conditions exhibited reliably positive levels of this oscillation pattern.

The brain LV (panels c and d) gives the distributed pattern of brain activity, and indicates at which electrodes and frequencies this LV was reliable. It comprises multiple frequencies including the theta and beta bands and involves numerous sites distributed across the scalp. Scalp saliences are nearly all positive, thus participants invoke additional power while studying subsequently

recalled pairs compared to subsequently not recalled pairs and compared to both recalled and not-recalled triples. The brain LV reveals higher-frequency theta-band activity (e.g., 6.73 Hz) over left lateral frontal sites and lower-frequency theta-band activity (e.g., 4.00 Hz) at lateral and posterior sites. Low-beta-band activity (e.g., 13.45 Hz) suggests bilateral dipoles over central sites and high-beta-band activity (e.g., 26.91 Hz) is focused at right anterior sites.

Behavior PLS (between-subjects approach)

Behavior PLS explains between-subjects variability in behavior (accuracy and RT) as a function of condition. This analysis identified two significant LVs, accounting for a total of 77% of the cross-block covariance.

Latent variable #1

The first LV (Fig. 3) accounted for 52% of the cross-block covariance. The behavior LVs (panels a and b) tell us how this pattern of activity covaried with performance across participants. Panels b and d plot the correlations between the brain LV and the respective behavioral measure. For all conditions, Accuracy-LV saliences were reliably positive while RT-LV saliences were reliably negative; thus, this LV was associated with good performance (i.e., high accuracy and fast response times). The brain LV (panels c and d) shows that this effect is predominantly within the theta band, focused over frontal sites, but includes some contributions from the beta band, also frontally.

Latent variable #2

The second LV (Fig. 4) accounted for 24% of the cross-block covariance. Turning to the behavior LVs we find that invoking this activity pattern was associated with better accuracy for both pairs

and triples regardless of subsequent memory (panel a). However, RTs were lengthened during all conditions. Because correlations with accuracy and RT are both positive, this suggests that this LV reflects a strategy with a speed–accuracy tradeoff (see Discussion). The brain LV (panels c and d) indicates that the oscillations implicated in this LV are predominantly in the delta band over posterior sites along with decreases in both beta and gamma oscillations over anterior central and lateral sites. Thus, the LV involves decreases in anterior delta and gamma activity with increases in posterior delta activity for increased accuracy at the expense of speed.

P_{episode} (f) spectra and oscillations in the raw trace

While the findings of the two PLS analyses are statistically reliable, one would like to know whether the patterns of oscillations they identified reflect common features of the raw

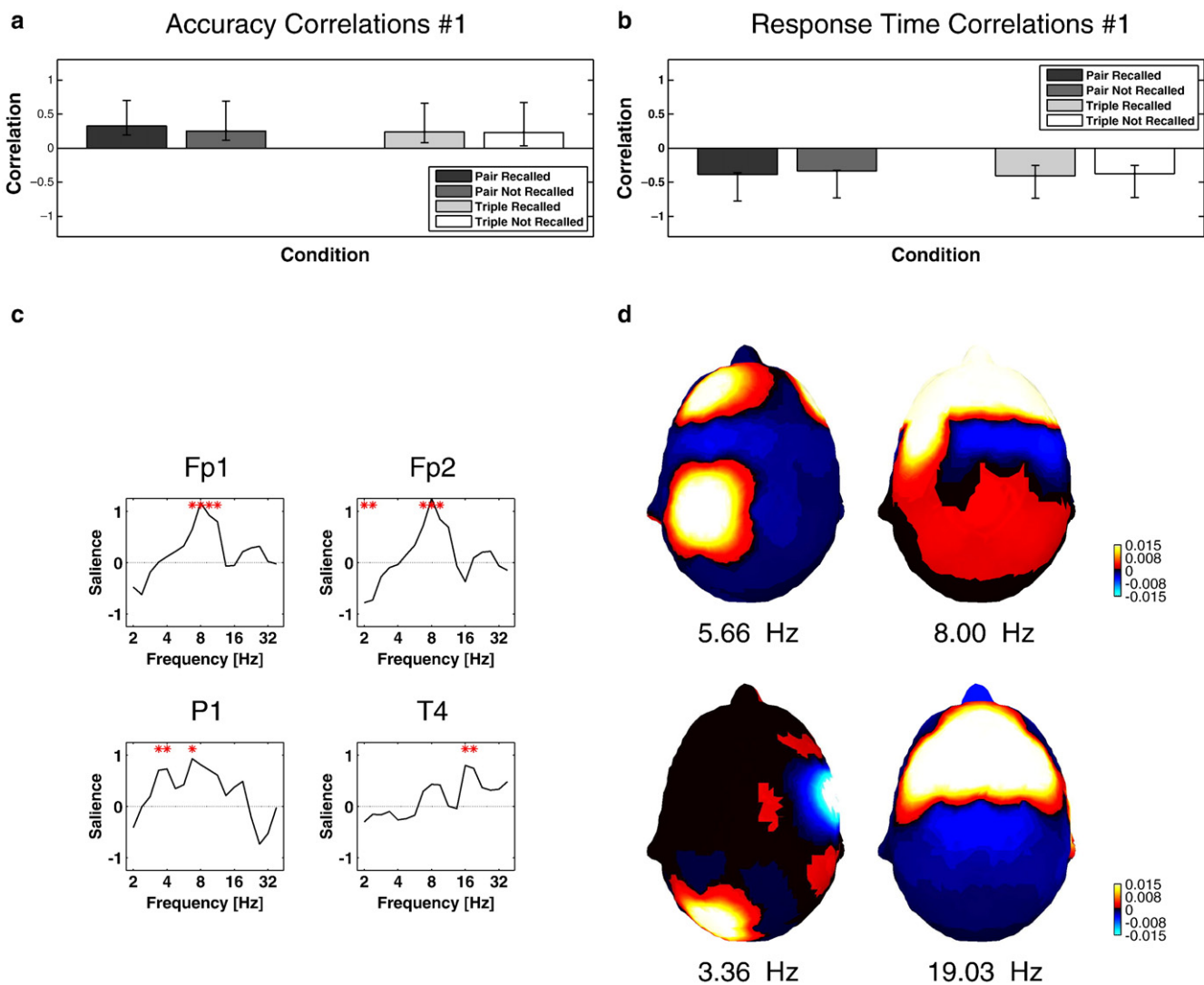


Fig. 3. Behavior PLS (between-subjects approach), Latent Variable #1. (a) Correlation between the brain LV and accuracy as a function of condition. (b) Correlation between the brain LV and RT as a function of condition. Error bars plot 95% confidence intervals. (c) Brain Latent Variable #1 at sample electrodes as a function of frequency. Red asterisks denote frequencies for which the saliency was reliable (bootstrap ratio > 1.96, equivalent to z scores with a p value of 0.05). (d) Topographic spline maps plotting saliency across the scalp at sample frequencies, wherever the bootstrap ratio magnitude exceeded a threshold of 1.96 (unreliable saliencies are plotted in black). Color scale denotes bootstrap ratio.

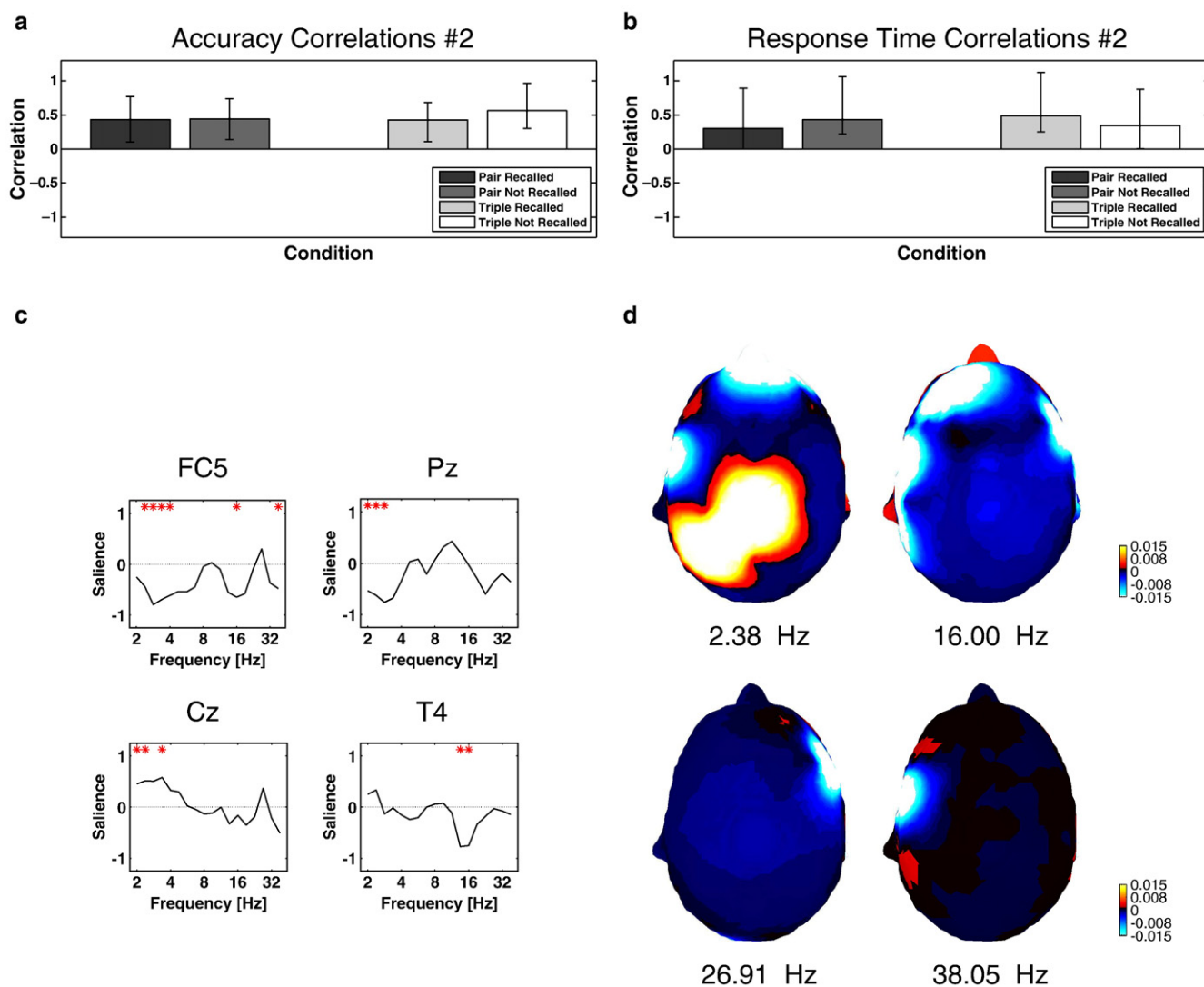


Fig. 4. Behavior PLS (between-subjects approach), Latent Variable #2. (a) Correlation between the brain LV and accuracy as a function of condition. (b) Correlation between the brain LV and RT as a function of condition. Error bars plot 95% confidence intervals. (c) Brain Latent Variable #2 at sample electrodes as a function of frequency. Red asterisks denote frequencies for which the salience was reliable (bootstrap ratio > 1.96, equivalent to z scores with a *p* value of 0.05). (d) Topographic spline maps plotting salience across the scalp at sample frequencies, wherever the bootstrap ratio magnitude exceeded a threshold of 1.96 (unreliable saliences are plotted in black). Color scale denotes bootstrap ratio.

EEG signal or rare, transient events. To assess this we can observe the $P_{\text{episode}}(f)$ plots at electrodes of interest. Fig. 5 shows that the oscillations analyzed by the two PLS analyses comprise from about 5–25% of the study time. Thus, these are not rare events but comprise a substantial proportion of the study signal.

Finally, theta oscillations are plainly visible in the raw, unfiltered record in intracranial recordings from rats (e.g., Bland, 1986; Vanderwolf, 1969) as well as humans (Caplan et al., 2001, 2003; Ekstrom et al., 2005; Kahana et al., 1999). However, whether theta rhythms appear as prominent oscillations in human scalp recordings is less clear. Some reports of human frontal midline theta during mental arithmetic did publish sample records showing theta oscillations in EEG records (Mizuki et al., 1980; Mizuhara et al., 2004; Mundy-Castle, 1951, 1957; Yamamoto and Matsuoka, 1990). We wanted to find out whether the rather prevalent segments of EEG identified by the oscillatory episode detection algorithm would appear like those classic records. Fig. 6

shows examples of raw EEG (the filter was that of the amplifiers plus a 60-Hz notch filter) that were identified by the oscillatory episode detection algorithm at electrodes and frequencies exhibiting reliable saliences in the Behavior PLS, LV 1. Thus, the theta oscillations we identified by the oscillatory episode-detection and PLS analyses are indeed features of the raw EEG record that are clearly identifiable as rhythmic activity.

Discussion

Partial least squares (PLS) analyses identified three spatio-spectral patterns of oscillatory activity related to study of word pairs and triples. Task PLS revealed a pattern of oscillations including the theta and beta bands that were specific to effective study of pairs (Fig. 2). Behavior PLS revealed frontal midline theta, along with oscillations at other frequencies, that covaried with good performance (Fig. 3). That analysis also revealed a

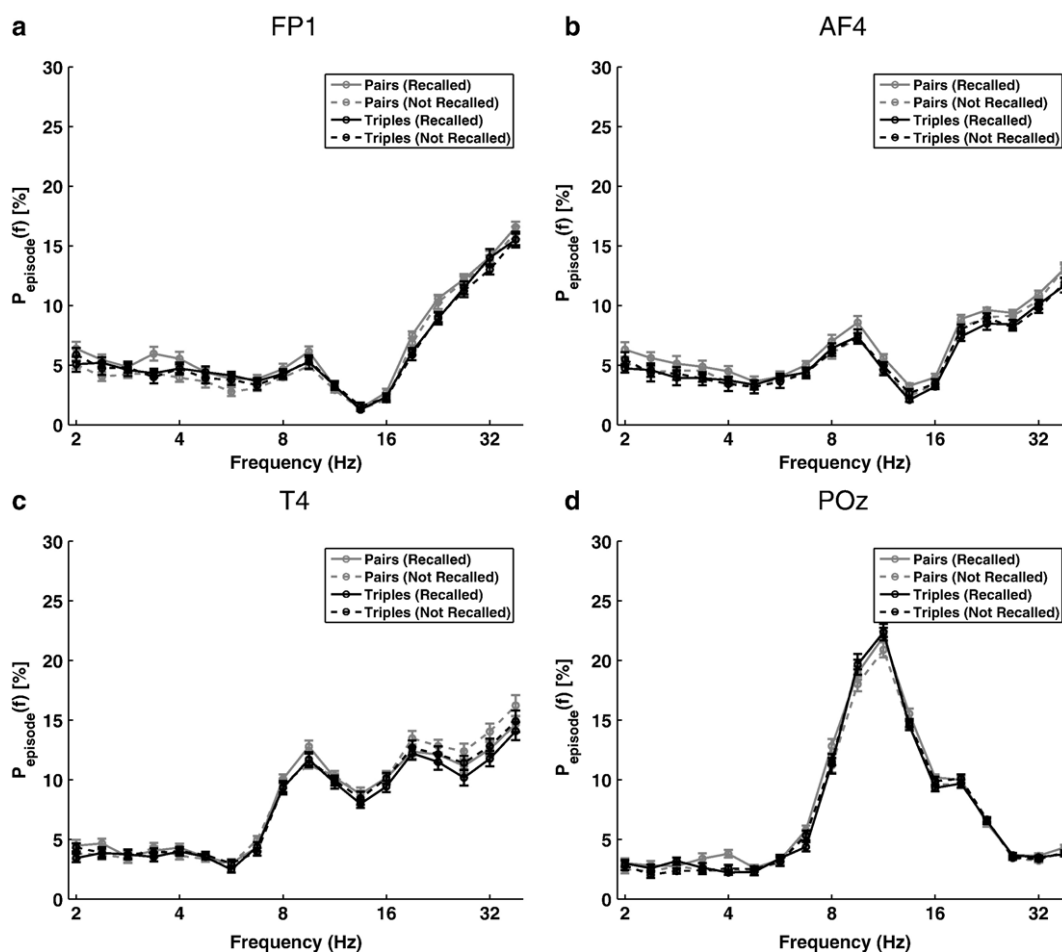


Fig. 5. $P_{\text{episode}}(f)$ spectra for example electrodes of interest. Error bars denote standard error of the mean across participants corrected for between-subjects variance (Loftus and Masson, 1994).

pattern involving delta and gamma oscillations that reflect a speed–accuracy tradeoff. We discuss each in turn.

Within-subjects activity for effective study of pairs

Task PLS identified a latent variable associated with effective study of pairs compared to other conditions (Fig. 2). This latent variable included contributions from several frequencies. Most prominent were the theta and beta bands. Theta-band power has been reported to exhibit a SME (Klimesch et al., 1996, 1997). Theta oscillations modulate long-term potentiation and depression (Hölscher et al., 1997; Huerta and Lisman, 1995; Orr et al., 2001; Pavlides et al., 1988) and fluctuations in their presence at study modulates conditioning rates in rabbits (Griffin et al., 2004); thus, this latent variable may reflect a physiological state necessary for effective learning of stimuli and their configurations (see also Caplan et al., 2001).

An alternative, non-memory explanation is also plausible. This pattern is similar to intracranial findings of theta along with beta oscillations most prominent over the central sulcus (Caplan et al., 2003). These prior findings revealed theta oscillations during a spatial learning task, but did not explain trial-to-trial variability in behavior and thus, it was proposed that those theta oscillations

relate to sensorimotor integration, one of the earliest proposed functions of theta (Bland, 1986; Bland and Oddie, 2001; Komisaruk, 1970). In the present task, this activity was recorded while participants were studying words but not making overt responses. Subvocal rehearsal is common in verbal memory tasks. Thus, the theta oscillations reported here might relate to subvocal rehearsal, requiring coordination of multiple brain areas analogous to sensorimotor integration but in the absence of actual motor responding (i.e., subvocal rehearsal), consistent with the experimental findings that motivated Bland's sensorimotor integration hypothesis (Bland, 1986; Bland and Oddie, 2001).

A further possibility is that the presence of theta oscillations has an inverse relationship with effective encoding, similar to recent findings from extracranial (Sederberg et al., 2006) and intracranial (Sederberg et al., 2007) recordings with measures of average power in free recall, a test of single-item memory. However, two things challenge this interpretation. First, the condition with higher levels of theta oscillations (namely, pairs) was more accurate, the reverse of this alternate hypothesis. Second, prior behavioral analysis and computational modelling using the pair/triple task dyad (Caplan et al., 2006) suggested that lower recall accuracy for triples is attributable to increased interference at time of test rather than differences in effectiveness of study (e.g., accuracy on triples was lower in a mixed-list

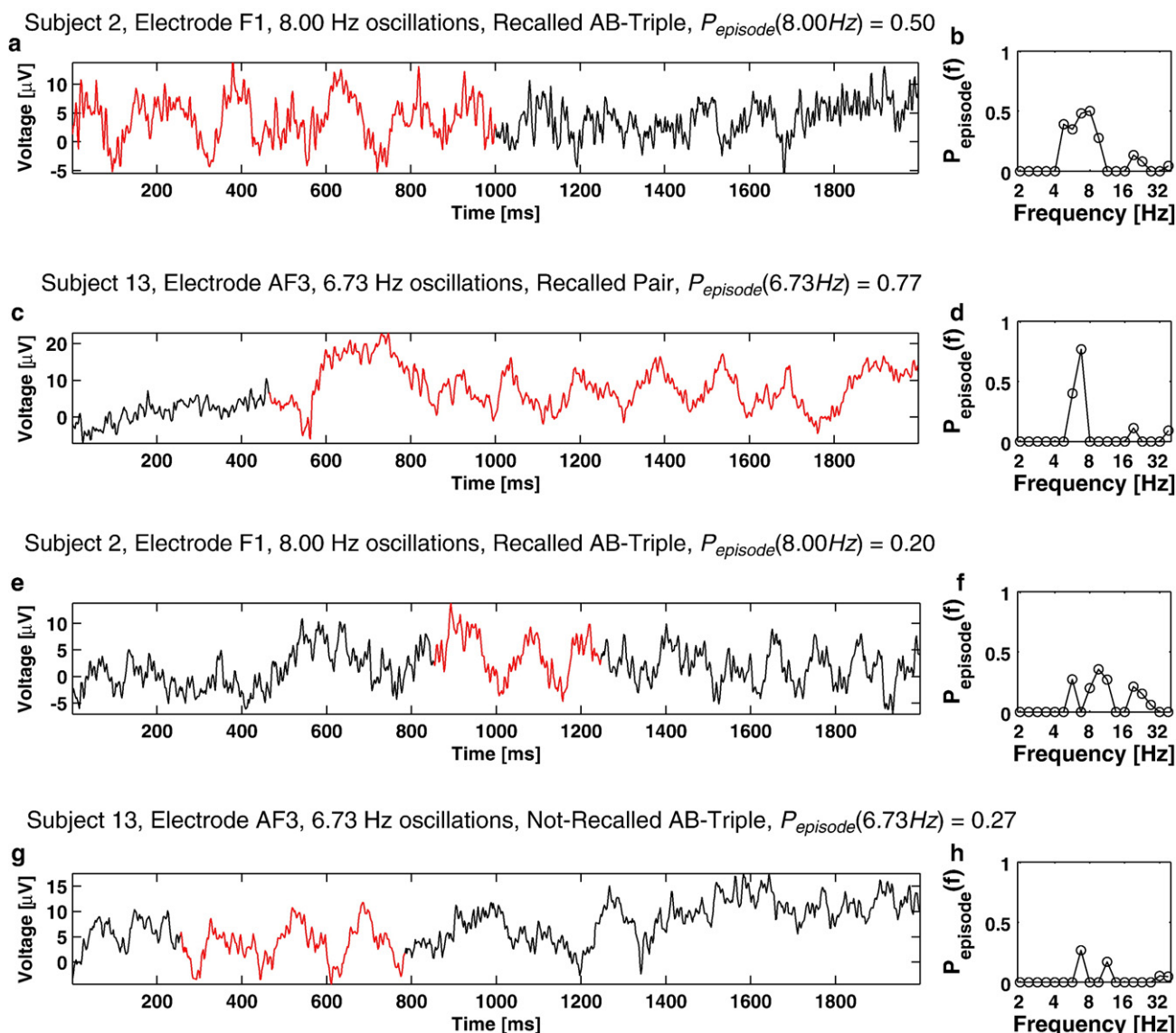


Fig. 6. Theta oscillations visible in the unfiltered EEG record for four example trials, two with high $P_{episode}$ (panels a–d) and two with lower $P_{episode}$ values (panels e–h). Panels a, c, e and g show raw traces of activity within a trial of interest; red-colored signal denotes signal times during which oscillatory episodes at the frequency of interest were detected. Panels b, d, f and h plot the $P_{episode}(f)$ values computed for the respective trial only. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

paradigm, in which pairs and triples were studied together and the subject did not know whether the upcoming words would form a pair or a triple).

Frontal theta and individual variability

The first latent variable of the Behavior PLS identified a pattern of oscillations that covaried with overall high accuracy and fast RTs for both pairs and triples (Fig. 3). The most prominent frequency band was the theta band, especially focused over frontal electrodes. However, it also included lateral beta oscillations and decreases in delta oscillations. It is important to note that this activity pattern differentiated high-performing participants from low-performing participants (between-subjects effect) but did not differentiate well studied pairs and triples from poorly studied pairs and triples, reminiscent of theta-band power correlations with

individual differences in (single-item) memory performance in humans (Doppelmayr et al., 2000) and rabbits (Berry and Thompson, 1978). It is also consistent with prior findings that while other frequency bands may covary with instantaneous memory demands, the theta band frequently does not (Caplan et al., 2001; Howard et al., 2003; Raghavachari et al., 2001). However, Summerfield and Mangels (2005) found frontal midline theta to be associated with good retrieval of associative information compared to item information alone. Other studies have found frontal midline theta to covary with memory load in item-memory tasks (Gevins et al., 1997; Jensen and Tesche, 2002; Onton et al., 2005). We suggest that the frontal midline theta contributing to the first latent variable of the Behavior PLS reflects the implementation of a strategy for effective learning of relational information, but equivalently for simple associations (pairs) and short lists (triples), without reflecting success or failure on any particular trial.

Oscillations related to rote processing

The Behavior PLS also identified a pattern of delta, beta and gamma oscillations that were increased for participants with more accurate but slower responses to both pairs and triples (second latent variable). This may reflect a study strategy with a speed–accuracy tradeoff, for instance rote rehearsal (as contrasted with elaborative processing), which would result in reduced accuracy but faster RTs for correct responses. This is consistent with findings implicating gamma oscillations in working memory maintenance (Lutzenberger et al., 2002; Tallon-Baudry et al., 1998, 1999) and increase with memory load in a short-term recognition task (Howard et al., 2003) perhaps reflecting activation of item representations.

Validity of the notion of theta

Is it appropriate to talk about theta as a distinct frequency band? In research with rats and rabbits, the hippocampal theta rhythm is exceptionally clear and easy to spot in unfiltered signal (e.g., Bland, 1986; Komisaruk, 1970; Vanderwolf, 1969) and can be defined not only based on frequency but also based on physiological properties. In humans, EEG is typically recorded at the scalp and theta is often not visible as an oscillation in the raw signal. Evidence of theta activity is generally more indirect, relying on Fourier analysis and planned comparisons that focus a priori on specific frequency bands of interest. Intracranial EEG recordings have confirmed that there are task-relevant theta oscillations that can dominate the raw signal in various areas of neocortex (Caplan et al., 2001, 2003; Kahana et al., 1999; Raghavachari et al., 2001) as well as in hippocampus (Ekstrom et al., 2005); these findings serve to demonstrate that visually striking, task-related theta oscillations can be found in the human brain. However, two questions remain.

Question 1: Are changes in theta-band power observed at the scalp related to underlying oscillations or non-oscillatory activity with similar spectral properties? Most research on oscillations in the human EEG has used measures of average power. According to Fourier's Theorem, any signal may be decomposed into a weighted sum of oscillations, but that does not mean the signal is best explained by those oscillations. To focus more exclusively on rhythmic signal, Caplan et al. (2001) developed the oscillatory episode detection method employed here. This method is conservative about labeling signal as oscillatory, requiring power to exceed a threshold (based on the background noise spectrum) and be sustained for a minimum of 3 consecutive cycles of wavelet coefficients. Fig. 6 suggests that this method does identify segments of signal that can even be dominant features of the EEG, bearing some qualitative similarity to intracranially recorded theta rhythms and to early reports of frontal midline theta (Mizuki et al., 1980; Mizuhara et al., 2004; Mundy-Castle, 1951, 1957; Yamamoto and Matsuoka, 1990) and other prominent rhythms such as the alpha rhythm (Berger, 1929). Thus, the present findings can be more aptly interpreted as oscillations and not simply increases in theta-band power.

Question 2: Does the theta band represent a distinct frequency band or is it part of a family of oscillations that can vary continuously across a broad band? Much of the human theta research, including intracranial findings, focuses only on a single frequency band such as theta (e.g., Guderian and Düzel, 2005; Kahana et al., 1999). This approach may have given the false impression that prior authors thought theta appears and acts somehow independent of activity at other frequencies. Other studies find similar effects in numerous

frequency bands (e.g., Caplan et al., 2001; Raghavachari et al., 2001; Sederberg et al., 2003) leaving open the question of how various frequencies relate to each other. On this question, Klimesch and colleagues (Klimesch et al., 1994; Klimesch, 1999) reported examples of band-specific modulations of theta and alpha that are anticorrelated, suggesting that theta and alpha reflect two mutually exclusive physiological states. Similarly, using PLS, Düzel et al. (2003) found theta and gamma power that covaried positively. The limitation of these studies is that they measured average power rather than rhythmic activity per se (see Question 1). The PLS method we applied to detected rhythmic activity is exploratory with respect to topography and frequency characteristics, thus not biased toward frequencies of interest. The resulting decomposition of the oscillation–behavior relationship identified a predominantly theta-band pattern of oscillations (Behavior PLS) but these were accompanied by beta or gamma oscillations, consistent with rat electrophysiology findings (Bragin et al., 1995), intracranial findings (Caplan et al., 2003; Sederberg et al., 2003) and models of theta (Borisjuk and Hoppensteadt, 1998; Fukai, 1999; Jensen and Lisman, 2005). This coupling of beta with theta oscillations is also strikingly similar to a recent report by Onton et al. (2005), showing that this dual-band pattern of activity increased with memory load during a recognition task.

The theta rhythm is thought to be induced at least in part by cholinergic modulation (Bland, 1986), and local increases in acetylcholine levels may enable a target region to overcome proactive interference (e.g., Caplan et al., 2007; De Rosa et al., 2004; Hasselmo and McGaughy, 2004). Thus, our theta oscillations (especially in the Behavior PLS, LV 1) may reflect cholinergic modulation that acts to resolve associative interference.

Neocortical interactions with the hippocampal theta rhythm

The hippocampus is thought to be involved in associative learning (e.g., Bunsey and Eichenbaum, 1996; Moses and Ryan, 2006; O'Reilly and Rudy, 2001; Rudy and Sutherland, 1989). The hippocampal theta rhythm in particular may be required for learning structured information (Buzsáki 2005; Jensen and Lisman, 2005). The topography of the study-related theta activity presented here suggests frontal generators. Hippocampal theta is thought to integrate activity in various cortical regions (Bland, 1986; Bland and Oddie, 2001; Komisaruk, 1970) and Jensen (2001) suggested how a theta-based phase code could transfer information from one brain region to another if both regions have synchronized theta. The theta oscillations reported here may coordinate with the hippocampal theta rhythm to learn relational information. This integrative function of theta is distinct, but not necessarily mutually exclusive with the possible local-plasticity effects described above.

Theta and memory for order

Some theories of the function of theta oscillations implicate this rhythm in learning not just of sets of items, but of their specific order (Adey et al., 1962; Buzsáki, 2005; Jensen and Lisman, 2005; McLardy, 1959). A natural prediction of such theories is that successful retrieval of order information should be associated with greater presence of theta oscillations at study, thus more theta oscillations during study of triples than pairs and during study of pairs than individual items, since cued recall consisting of single-item probes relies on whether the participant can recover order information for triples but not for pairs. Our findings do not

support the notion that theta oscillations specifically preserve order information, because theta contributes to the first latent variable of the Behavior PLS similarly for pairs and triples. Theta oscillations comprise part of the Task PLS latent variable as well, but this activity was specific to successful study of pairs. This is in contrast to time-domain analyses which have identified nonrhythmic brain activity that facilitates subsequent performance on triples but not pairs (Caplan et al., submitted for publication). Thus, our findings are consistent with theta oscillations supporting learning of relational information, but speak against the notion that sequentially ordered lists are a privileged form of relational information with respect to the function of theta. An important caveat is that theta oscillations originating in the hippocampus or other limbic areas may support the proposed order-specific functions of theta while producing sources that are difficult to detect at the scalp.

Unified models of associative and serial list memory

Certain classes of memory models treat either paired associates learning or serial list learning alone, implying that a distinct model is required to account for each paradigm whereas others account for memory for pairs and memory for serial lists using the same underlying cognitive processes (Ebbinghaus, 1885/1913; Lewandowsky and Murdock, 1989) supported by behavioral evidence (Caplan, 2005; Caplan et al., 2006). However, physiological activity reflecting relevant cognitive processes could tell a different story. Indeed, time-domain analyses of the present data set already suggested that participants may invoke study strategies to differing degrees or with different implications for subsequent memory performance (Caplan et al., submitted for publication). Study processes may differ in how precisely order information is stored; for example, forming visual imagery may result in accurate retrieval of the pairings of items but with poorer order information compared to constructing sentences involving multiple items in which the grammar constrains the items' order to accurately replicate their initial presentation order. Still, most of the behaviorally relevant study activity identified using the multivariate PLS method pointed to commonalities rather than differences between the two paradigms. The present findings tell a similar but complementary story. Task PLS identified a multi-frequency pattern of oscillations that were specific to well recalled pairs, suggesting first, that participants invoke this oscillatory pattern to a greater degree for pairs than for triples, and second, that the cognitive process associated with these oscillations influences subsequent recall accuracy for pairs but not for triples. However, both Behavior PLS latent variables identified patterns of oscillations that predicted behavior similarly for triples as for pairs, suggesting that a substantial portion of the crucial study processes are shared between the two paradigms. Thus, cognitive models must be able to incorporate the dissociation identified in LV 1 of the Task PLS, but they may remain largely parsimonious by reusing cognitive processes between two classic behavioral memory paradigms.

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