

Decoding oscillatory representations and mechanisms in memory

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ARTICLE INFO

Available online 4 May 2012

Keywords:

MEG

EEG

Pattern classification

Episodic memory

Working memory

Priming

Negative priming

ABSTRACT

A fundamental goal in memory research is to understand how information is represented in distributed brain networks and what mechanisms enable its reactivation. It is evident that progress towards this goal will greatly benefit from multivariate pattern classification (MVPC) techniques that can decode representations in brain activity with high temporal resolution. Recently, progress along these lines has been achieved by applying MVPC to neural oscillations recorded with electroencephalography (EEG) and magnetoencephalography (MEG). We highlight two examples of methodological approaches for MVPC of EEG and MEG data that can be used to study memory function. The first example aims at understanding the dynamic neural mechanisms that enable reactivation of memory representations, i.e., memory replay; we discuss how MVPC can help uncover the physiological mechanisms underlying memory replay during working memory maintenance and episodic memory. The second example aims at understanding representational differences between various types of memory, such as perceptual priming and conscious recognition memory. We also highlight the conceptual and methodological differences between these two examples. Finally, we discuss potential future applications for MVPC of EEG/MEG data in studies of memory. We conclude that despite its infancy and existing methodological challenges, MVPC of EEG and MEG data is a powerful tool with which to assess mechanistic models of memory.

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1. Introduction

In this review article, we will focus on how multivariate pattern classification (MVPC) based analyses of electromagnetic data can be used to further our understanding of memory mechanisms. Since we cannot cover this topic in its entirety we will focus on two questions within this larger theme by referring to two recent publications (Newman, & Norman, 2010; Fuentemilla, Penny, Cashdollar, Bunzeck, & Duzel, 2010). How do representations differ across memory types and how does their representational strength affect memory performance (also see Newman, & Norman, 2010)? How are memory related representations dynamically reactivated when needed (also see Fuentemilla et al., 2010)?

Specifically, we will discuss how the implementation of MVPC to study memory replay can further our understanding of the mechanisms that underlie offline working memory maintenance

(i.e., Fuentemilla et al., 2010) and episodic memory. We will also discuss the possibilities that the MVPC approach offers in understanding how representational strength at information encoding affects different types of memory processes, such as perceptual priming and conscious recognition memory (i.e., Newman, & Norman, 2010). These two studies differ in the features of electrophysiological information they used for MVPC. We therefore believe that their comparative discussion in this review will help to illustrate the ample possibilities that MVPC can provide for investigating time-specific neural processes in memory.

In both studies (Fuentemilla et al., 2010; Newman, & Norman, 2010), MVPCs were trained on spectral amplitudes of oscillations and hence this type of analysis will be the focus of this review. Oscillatory fluctuations of local field potentials are held to play a mechanistic role in various aspects of memory including the representation and off-line maintenance of events and sequences of events, the assessment of novelty, the induction of plasticity during encoding, as well as the consolidation and the retrieval of stored memories (for a review see Duzel, Penny, & Burgess, 2010). Recent findings indicate that oscillatory mechanisms identified in rodent studies have significant parallels in the neurophysiology of human memory (for a review see Duzel et al., 2010). Hence,

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combining MVPC based decoding approaches with measures of brain oscillations seems particularly appealing for a mechanistic investigation of human memory function. Although we focus here on amplitude measures of oscillations, in principle, MVPCs could also be conducted using other types of information such as oscillatory phase or phase-coupling (e.g., [Gysels, & Celka, 2004](#)).

Before we discuss how MVPC can contribute to our understanding of memory processes, we will outline the basic methodology of EEG/MEG based MVPC analyses and highlight key constraints that are imposed on MVPC when classification is based on oscillatory brain activity. Specifically, we will touch upon the temporal resolution of MVPC and potential approaches that can be taken to appropriately select or reduce the oscillatory brain activity features that are used to train classifiers. Furthermore, we will briefly highlight problems associated with baseline correction of EEG and MEG data from the possible vantage point of feature representations in the baseline period.

2. Methodological considerations

When implementing MVPC on MEG/EEG recordings, the data preparation and pattern classification steps require certain considerations which we will highlight in here.

2.1. Time-resolution

Research questions and hypotheses can pose different constraints on the temporal resolution of decoding. For instance, restricting MVPC to oscillatory activity in higher frequencies such as beta (13–25 Hz) and gamma (25–140 Hz) will provide better temporal resolution as compared to MVPC that also includes alpha (8–12 Hz) and theta (4–7 Hz) oscillations. A restriction of MVPC to higher frequencies can be adequate for testing neural mechanisms related to memory replay, such as theta-coupled replay. For this type of analysis, it is important that the temporal resolution of decoding should be higher than half of the duration of a theta-cycle (for a 5 Hz wavelet, this should be higher than 100 ms). In addition to constraining the feature space to frequencies higher than theta (for instance to neural oscillations in the beta and gamma frequency range, see below), this can be achieved by using frequency decomposition methods that have high temporal resolution. In case of wavelet-transformation, this can be achieved by using wavelets with fewer cycles. We believe that 5 to 7 cycle wavelets provide an acceptable compromise between time and frequency resolution. More cycles may improve decoding by improving frequency resolution but could potentially compromise the ability to detect theta-coupling of replay. If, on the other hand, the research question at hand requires a fuller characterization of neural representations of experimental stimuli, it can be appropriate to include lower frequencies (theta and alpha) into MVPC and use longer wavelets that provide better frequency resolution. This approach will decrease temporal resolution, but will increase feature space and improve the separation of frequency features so as to best characterize the differences between representations (however see [Newman and Norman \(2010\)](#) for a discussion of potential smearing of MVPC performance into the baseline period with long wavelets and low frequency bands).

2.2. Baseline correction and spectral power normalization procedures

Most studies of EEG and MEG normalize data with respect to the “baseline” immediately preceding stimulus-onset. This single-trial baseline correction, however, can potentially compromise

classification accuracy. This is because the baseline period is not devoid of information. It is likely that information related to some form of prediction or expectation of the upcoming stimulus or the continued rehearsal of the previously seen item may be present. Depending on the exact nature of the experiment, some types of baseline selection could improve or corrupt classification. For instance, in a random sequence of A and B (e.g., AABBBBBAAAA-BABB), approximately half of the A trials are preceded by A and the other half are preceded by B. If there is rehearsal of the preceding item (A or B) in the baseline periods of A, single-trial baseline correction would confound half of the A stimuli with (baseline) representations related to B and vice versa. This could compromise classification accuracy. Therefore, it may sometimes be more appropriate to think about alternative methods of baseline correction (e.g., taking running averages of baselines of neighboring items of A) or to avoid baseline normalization altogether. In the example shown in [Fig. 1](#), comparing face and scene stimuli, baseline correction was only conducted during data pre-processing as an offset correction. However, after frequency transformation, there was no additional baseline correction and instead the power at each time-point, frequency and channel was z-normalized across trials (as in [Newman, & Norman, 2010](#)). In our hands, z-normalized classification without baseline correction led to better classification accuracy than after single-trial baseline correction (unpublished observations).

2.3. Feature selection

The data in each trial of an MEG/EEG experiment has three dimensions: time, frequency and channels/sensors. In the approaches that we have highlighted so far, each classifier was initially trained on only two dimensions, frequency and channel features. Time information has so far not been used as feature (although this should be possible in principle, e.g., [Polan, Paulus, & Nitsche, 2011](#)) and instead, a different classifier has been trained at each relevant time point. Although, in this approach, time is not part of the feature space, the number of features that can be potentially used for training a classifier can still be very large (e.g., with a modern whole-head MEG system, 274 sensors and 40 frequency bands there are 10,960 features per time point).

Feature selection refers to methods that reduce the number of features by changing the feature space and/or selecting the relevant features in order to facilitate robust classification. One simple feature selection method is a conceptual a priori restriction of frequency space. For example, in the decoding approach used in [Fuentemilla et al. \(2010\)](#), the goal was to test the hypothesis that reactivation of memory representations is phase-locked to slow oscillations in the theta-frequency range. Hence, it is evident that MVPCs trained to detect representations should not include features in the theta frequency range and should be restricted to those fast frequencies (beta and gamma) that are hypothesized to be phase-coupled with theta. In contrast, when investigating the representational characteristics of stimuli in memory, it is more appropriate to include as many features as possible into MVPC and thus achieve a comprehensive coverage of neural activity patterns that are involved in representation. In the paper by [Newman and Norman \(2010\)](#) the goal was to understand how information representation at encoding determines a specific form of priming. Here, it was more appropriate to train MVPCs without an a priori restriction and hence to include both slow and fast oscillations.

A second possibility for feature selection is to restrict sensor/electrode space on the basis of prior anatomical hypotheses. Here, assumptions regarding the neural sources that may differentially represent two categories of interest can be used to weight or restrict sensors/electrodes used for MVPC. Hence, instead of using

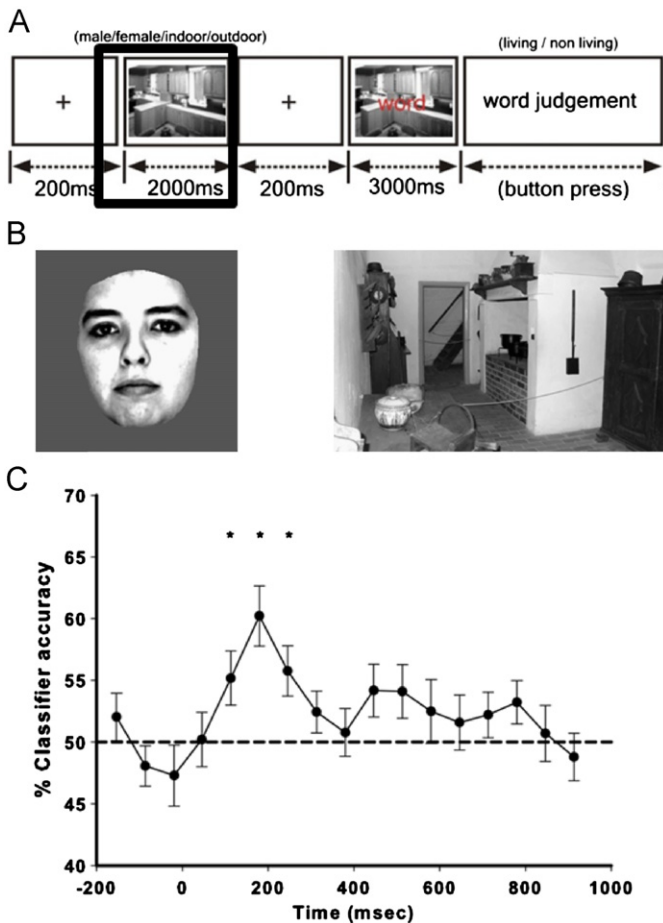


Fig. 1. Example for a MVPC of MEG data. An associative recognition experiment was performed by 11 subjects. This experiment consisted of two phases, encoding and retrieval and MVPC data from encoding are displayed here. (A) At the encoding phase subjects saw images of faces (50%) or scenes (50%) for 2000 ms and then a word displayed on top of each image. They were asked to try to remember the association between the image and the word. Afterwards subjects indicated if the word denoted a living or nonliving category (to induce deep processing). At each encoding run, 20 image-word pairs were presented. (B) An example of a scene and a face image. (C) We trained pattern classifiers for each of the 11 participants to classify the MEG oscillatory patterns recorded when the images were presented on the screen (bold square) into faces and scenes. 17 time-windows (centered at: -153, -87, -20, 47, 113, 180, 247, 313, 380, 447, 513, 580, 647, 713, 780, 847, and 913 ms relative to picture onset) were selected and MEG time-frequency features from each time window was used to train a separate classifier (hence 17 different classifiers were trained). The frequency range for each classifier was 8 to 45 Hz and this range was divided into 38 frequency steps. Oscillatory power at each frequency, channel, and time point was z -normalized across trials. The data set consisted of 60 faces and 60 scenes per participant. MVPC was conducted using non-linear neural network classification (for details see main text). For each classifier we adopted a 10-fold cross-validation procedure where one tenth of the pictures from each category were removed from the training set for testing and the model was trained on the remaining pictures. Prior to training the pattern classifiers, a feature selection step was conducted by performing a two-tailed paired t -test ($p < .05$) on each MEG feature (38 frequencies, 274 MEG channels and 21 time-points within each time-window) to detect features that were different between the two categories. Importantly, the feature selection procedure was conducted at each cross-validation iteration excluding testing trials. The trained classifier was then used to predict the category of the left-out trials. This procedure was repeated for each of the ten folds. Classifier accuracy was calculated by averaging performance across the 10 train-test folds. The plot demonstrates the average MVPC accuracy across subjects. Error bars represent the standard error, * $p < .05$.

all sensors or electrodes, this method would involve selecting/weighting only those that are likely to detect activity from those brain regions. This type of feature selection can be achieved using various source modeling tools (Barnes, Litvak, Brookes, & Friston,

2011). Alternatively the feature space can be reduced by data reduction methods such as Principal Component Analysis (Bishop, 2006; e.g., Manning, Polyn, Baltuch, Litt, & Kahana, 2011).

Once the frequencies and sensors/electrodes that are entered into MVPC are specified, data-driven feature selection steps can follow. One possibility is to use a univariate statistic at each sensor and time-frequency step in order to select those features that would constitute the independent variables (i.e., the inputs) for MVPC. Features (spectral amplitude at particular time-frequency steps and sensors/electrodes) can be selected if they are significantly different between categories of interest. Alternatively, Bayesian inference can be used for selecting the most relevant features (Tipping, & Faul, 2003; van Gerven, Cseke, de Lange, & Heskes, 2010).

It is important to note that this data-driven feature selection step should not involve any data from the testing set. For instance, in the Fuentemilla et al. (2010) study, feature selection was conducted on all trials presented during encoding, but MVPCs were used to classify delay activity later on. If the goal of that study would have been to make inferences on how representations at encoding relate to subsequent memory or for validating the MVPC performance, data driven feature selection should have been performed separately in each cross-validation iteration, thus excluding the testing data set (see Fig. 1 as an example).

2.4. Pattern classification algorithms

In previous EEG and MEG studies of memory, non-linear neural network (NN) classification (Fuentemilla et al., 2010) and ridge regression (Newman, & Norman, 2010) have been used for classification. Various other classification algorithms (Fig. 2) can, in principle, be used to classify EEG/MEG data. Some of the well-known classification algorithms include K -nearest neighbor, General Linear Model based classification, Support Vector Machines, Linear discriminant analysis (Bishop, 2006) and Sparse Bayesian Classification (Tipping, & Faul, 2003). A formal comparison as to how these different classifiers perform for a given experimental EEG/MEG data set is beyond the scope of this paper.

An example for the implementation of a neural network classifier can be found in Fuentemilla, et al. (2010). In that study, the neural network topology was defined by an input layer, which contained each of the sensor/frequency features, a hidden layer comprising four units, and an output layer, defined by two units, one for each of the category-specific patterns (e.g., the output pattern of [1 0] for indoor scenes versus [0 1] for outdoor scenes). Each unit in the hidden and output layers had a bias vector. The weights of the connections were initialized from a zero mean, unit variance isotropic Gaussian distribution. The new input was assigned to a class according to the number generated in the output unit. Neural network optimization (i.e., learning) was based on the conjugate gradient algorithm ("traincgb" in Matlab) (Bishop, 1995) implemented with the Matlab Neural Network Toolbox (Mathworks) and some of the software routines available from the Princeton Multi-Voxel Pattern Analysis for fMRI website (<http://www.pni.princeton.edu/mvpa>) but modified and adapted to MEG data and extended by new analysis scripts. For methodological aspects of cross-validation see Newman and Norman (2010), Fuentemilla et al. (2010). Fig. 2 schematically illustrates the steps required for implementing MEG/EEG based pattern classification.

3. Working memory maintenance (theta-coupled replay)

The first example for an EEG/MEG based decoding approach to memory that we would like to highlight, aims at understanding the neural processes that enable working memory, the ability to

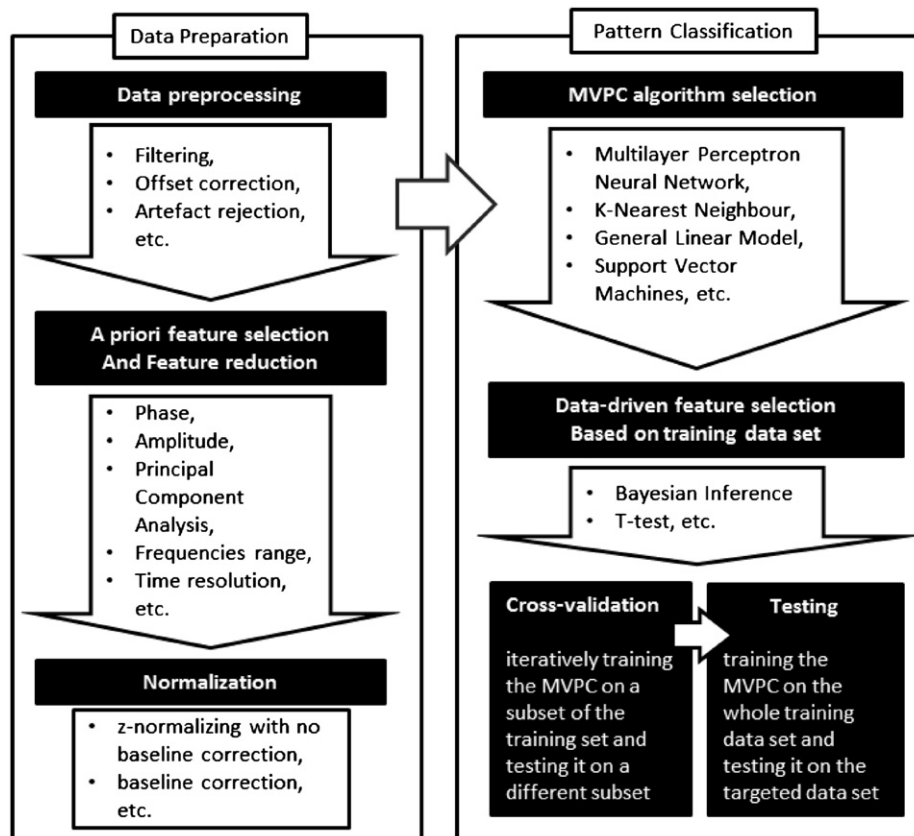


Fig. 2. Schematic illustration of the steps involved in the implementation of pattern classification using MEG/EEG data.

actively maintain and manipulate information over short periods of time (for a review see [Baddeley, 2010](#)). Here, we focus on a specific aspect of working memory, namely active maintenance of information during delay periods. Given the high temporal precision of EEG/MEG recordings, this approach can be suitable to scan the maintenance delay period for instances of replay of working memory content and characterize the timing and periodicity of these replay instances. As mentioned above, such an approach necessarily requires a priori assumptions regarding the neural mechanism that may enable replay. For instance, if the neural mechanisms of interest are those that vary rapidly within milliseconds, the decoding algorithm used to detect replay should be restricted to fast oscillations in the beta or gamma frequency band. A prototypical example for this set of questions has to do with the role of hippocampal–cortical interactions for replay, namely enabling theta-coupled reactivation on the basis of theta-beta/gamma cross-frequency coupling (for a review see [Duzel et al., 2010](#)). The key assumption here is that rapidly enacted instances of cortical reactivations ('replay') are temporally biased by slow (theta) oscillations coordinated by the hippocampus. For this type of question then, classification of EEG/MEG signals should be conducted using a feature space that is restricted to beta and gamma (and possibly also alpha) oscillations. Hence, here only those features of memory representations are of interest, which are signaled with oscillations faster than theta oscillations ([Fig. 3](#)).

Although we will discuss this approach primarily in relation to working memory maintenance, it is also well suited to investigate the neural mechanisms underlying episodic memory, the ability to retrieve the contextual details of past events after long periods of time ([Tulving, 1972; Tulving, 1985](#)) (see [Fig. 3](#)). Working memory and episodic memory, are often thought to be functionally distinct. However, recent conceptualization of how memory is organized in

the brain (for reviews see [Nadel, & Hardt, 2011; Duzel, et al., 2010](#)) suggests that for certain types of information these two forms of memory may share similar mechanisms, despite the fact that they operate over very different retention intervals.

Observations that point in this direction come from studies on associative relational, or configural–relational memory, for instance memory for object–location associations, or memory for the topographic layout of scenes (for a review see [Cashdollar, Duncan, & Duzel, 2011 and Nadel, & Hardt, 2011](#)). Patients with bilateral hippocampal injury who have severe deficits in episodic memory are also impaired in short-term memory tests involving this type of material even if the retention interval is only a few seconds ([Cashdollar et al., 2009; Hartley et al., 2007; Hannula, & Ranganath, 2008; Baddeley, Allen, & Vargha-Khadem, 2010](#)). A number of imaging studies have also supported this possibility. For example, fMRI studies have shown increased activity in the hippocampus and surrounding MTL areas during the delay period of delayed-match to sample (DMS) tasks ([Ranganath, & D'Esposito, 2001; Stern, Sherman, Kirchoff, & Hasselmo, 2001; Hasselmo, & Stern, 2006](#)). Furthermore, an MEG study showed interareal theta synchrony patterns during the delay period of DMS involving configural–relational scene information and that such synchrony was absent in patients with bilateral hippocampal injury in conjunction with their behavioral impairment in this task ([Cashdollar, et al., 2009](#)).

Importantly, the behavioral working memory deficit associated with bilateral hippocampal injury in itself does not provide an insight into the mechanisms underlying short-term memory retention of configural–relational information. Indeed, the behavioral findings on their own are not sufficient to conclude that the hippocampus may be critical for the active maintenance of relational or topographic forms of visual information in working memory. Instead, the behavioral observation that patients with

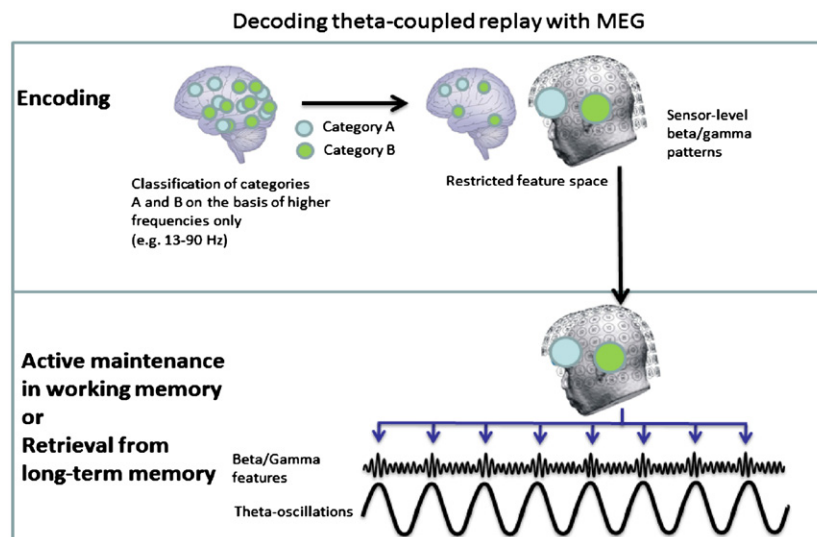


Fig. 3. Detecting theta-coupled memory replay in working memory and episodic memory using MVPC. First an a priori restriction of feature space is performed by excluding lower frequencies (i.e., theta), followed by MVPC training on data from the encoding phase. The trained classifiers are tested on data from the subsequent delay maintenance period (in case of working memory) or subsequent retrieval phase (in case of episodic memory). The instances of stimulus/category-specific “replay” are related to the phase theta oscillations (during maintenance or retrieval) to test whether replay is coupled to the phase of theta oscillations. It should be noted that this type of approach is agnostic as to whether phase-coupled reactivation of information entails temporal information about the encoding episode (such as a particular sequence of viewing objects displayed in a given scene).

hippocampal lesions have impaired short-term memory could also be interpreted as showing that relational information is encoded into long-term memory and must be subsequently retrieved from long-term memory even after a brief delay (without any intervening active maintenance process).

One candidate physiological mechanism for how the hippocampus can coordinate cortically distributed information replay during the delay period relies on network oscillations (Buzsáki, & Draguhn, 2004). Theta and gamma oscillations are held to play a mechanistic role in enabling this coordination (Jensen, & Colgin, 2007; Sirota et al., 2008; Lisman, 2010). One central hypothesis is that memories are replayed through phase-locking distributed neocortical gamma oscillations to hippocampally coordinated theta oscillations (Sirota, et al., 2008; Jensen, & Colgin, 2007). Such cross-frequency coupling of hippocampally generated slow oscillations and cortically generated fast oscillations could be a common mechanism enabling memory replay in both working memory and episodic memory (Sirota, et al., 2008; Jensen, & Colgin, 2007; for a review see Duzel, et al., 2010). It should be noted that, from a computational point of view, theta-gamma coupling could also support working memory mechanisms that are not dependent on the hippocampus (Jensen, 2006), but is suitable to account for hippocampus-dependent working memory (Jensen, & Lisman, 2005; Lisman, 2010).

Testing this hypothesis is a challenging endeavor because available imaging tools and analysis methods have profound limitations. Clinically motivated invasive electroencephalography (EEG) recordings (in patients undergoing evaluation for epilepsy surgery) allow direct measurement of hippocampal LFPs with high temporal and spatial resolution, but within-subject spatial sampling of distributed cortical activity patterns is severely limited and determined by clinical considerations. fMRI does neither have the temporal resolution nor the frequency resolution required for this specific question.

3.1. Testing replay in working memory using MEG based MVPC

MVPC based analysis of human MEG data recently helped to overcome these limitations (Fuentemilla, et al., 2010). We

exploited the fact that MEG (and EEG) recordings allow sampling of brain activity including most of the neocortical mantle simultaneously and may therefore be better suited to comprehensively track memory replay involving distributed representations. Using a configural-relational DMS task (Cashdollar, et al., 2009), MVPC decoding algorithms were trained on the oscillatory brain response (beta and gamma oscillations) to the visual presentation of images recorded with MEG (Fuentemilla, et al., 2010). These classifiers were applied to brain activity associated with subsequent maintenance of the scenes during a 5 s delay interval.

In the experiment (Fuentemilla, et al., 2010; Cashdollar, et al., 2009), a sample is presented for 3 s and this is followed by a delay period in which a fixation point is presented on a grey background. This is followed by a recognition test for the sample, where two probes are presented one of which is identical with the sample. The participant has to identify via a button press on which side of the screen the identical stimulus (matching probe) is located. There are three 6-min blocks of non-configural maintenance trials, where the two probe stimuli are highly dissimilar, and three 6-min blocks of configural maintenance trials, where the two probe stimuli are very similar. This configural maintenance condition was thought to require the maintenance of more perceptual detail to correctly identify the match between sample and probe. Another three 6-min blocks required a hard perceptual discrimination between the two probes. Here, participants are told that no decision will be required regarding the sample when the two probes are presented. The task here is merely to decide whether the two probe stimuli are identical or not. This control condition served as a no-maintenance condition. It was also designed to ensure that any activity during the delay period was not related to the anticipation of, or preparation for, a difficult discrimination between probes. In all conditions, half of the samples depicted indoor and the other half depicted outdoor scenes. MVPCs were trained on the MEG data at encoding to discriminate indoor and outdoor scenes (Fuentemilla, et al., 2010). The MVPCs were then used to track the replay of sample information during maintenance.

Using this approach, replay was detected during the entire delay maintenance interval. Replay was specific to whether the

maintained image depicted an indoor or an outdoor scene and whether maintenance centered on configural–relational associations of scene elements or just single scene elements. The periodicity of replay events was coordinated by the phase of theta oscillations, such that replay of the sample occurred at the same phase of each theta cycle, and the amount of theta-coordination was correlated with the accuracy of working memory performance in the configural–relational condition. This coordination reflects theta-gamma coupling (and also theta-beta coupling) thus confirming the predictions of a mechanistic model of working memory maintenance and linking such coupling to behavioral performance in humans (Fuentemilla, et al., 2010). Importantly, demonstrating such periodic replay non-invasively would not have been possible without the use of MVPC techniques on MEG data.

Compatible evidence that cross-frequency coupling of oscillations mediates a phase-dependent coding of items during maintenance in right frontal regions comes from a recent study in non-human primates (Siegel, Warden, & Miller, 2009). This cross-frequency interaction may not only be involved in sequential information processing but also in object-space representations, as has been described in rat hippocampus (Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009).

3.2. Hippocampal and prefrontal theta oscillations coordinate replay

According to the aforementioned lesion evidence that bilateral hippocampal injury impairs performance in the configural–relational version of this task and the theta phase-coding mechanism proposed by Lisman and colleagues (Jensen, & Lisman, 2005; Lisman, 2010), the hippocampus should be one of the generators of the theta rhythm that phase-coordinates the replay of beta/gamma events (Sirota, et al., 2008). Recent research in rodents demonstrates that neurons in the medial prefrontal cortex show phasic firing relative to hippocampal theta rhythm when navigation through a T-maze requires the maintenance of a goal and target location in working memory (Jones, & Wilson, 2005). In one study, approximately 40% of units in the medial prefrontal cortex (mPFC) were phase-locked to the hippocampal CA1 theta rhythm. CA1-mPFC entrainment was specific to 4–12 Hz and was evident at every level examined, including individual pairs of co-active neurons, theta phase-locking of neurons to theta local field potentials (LFPs), and hippocampal–prefrontal theta LFP coherence (Jones, & Wilson, 2005). This finding points to a possible organizing role for hippocampal theta-patterned output in hippocampal–neocortical synchronization (Jones, & Wilson, 2005).

Testing this anatomical hypothesis requires investigating which brain regions were involved in generating the theta oscillations that coordinated the periodic replay of configural–relational information. A follow-up investigation (Poch, Fuentemilla, Barnes, & Duzel, 2011) of the data published by Fuentemilla, et al. (2010) used a beamformer algorithm to produce estimates of regional theta rhythms and constructed volumetric images of the phase-locking between the local theta cycle and the instances of replay (detected in the 13–80 Hz band). This study found that individual differences in DMS performance for configural–relational associations were related to the degree of phase coupling of cortical replay to theta oscillations generated in the right posterior hippocampus (for other studies that have reported hippocampal activity using MEG and for a discussion of the limits of this technique see Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Quraan, Moses, Hung, Mills, & Taylor, 2011; Kaplan et al., 2012) and the right inferior frontal gyrus. This confirmed the prediction that the timing of memory replay in humans is phase-locked to the hippocampal theta rhythm.

Together, these data might plausibly be accounted for by taking a representational perspective to hippocampal memory

contributions (e.g., Nadel, & Hardt, 2011, also see Saksida, & Bussey, 2010). According to this view the replay (or reactivation) of associative/relational memories relies on the hippocampus, irrespective of whether the retention interval is short or long. The hippocampus may therefore be necessary to bind and integrate information about different object features and spatial layout that are individually represented in different portions of the ventral visual stream and the medial temporal lobe (MTL) (Eichenbaum, Yonelinas, & Ranganath, 2007). Such binding would occur during encoding and then again during later replay irrespective of whether replay occurs only after a few seconds or after minutes or hours (note that with very long retention intervals, systems level consolidation processes may potentially change the nature of the original representation (McClelland, McNaughton, & O'Reilly, 1995; Moscovitch et al., 2005) and consequently reactivated and encoded memory content may be somewhat different between each other.)

4. Different types of representations in memory

The second example for MEG/EEG based MVPC that we would like to highlight focuses on the nature of memory representations and does not restrict feature space due to a priori assumptions underlying the physiological mechanisms enabling reactivation. The goal of such an approach is to describe memory representations as completely as possible so as to enable detecting how they contribute to different forms of memory such as priming, familiarity, recollection or semantic memory. Hence, in this type of approach, EEG/MEG classification is not restricted to certain frequency bands, but instead broadened to also include slower oscillations such as theta and delta (<4 Hz). Newman and Norman (2010) illustrated this approach in a study which assessed the degree to which the activation of a particular representation (i.e., representational “strength”) affects subsequent memory performance.

Newman, and Norman (2010) focused on the degree to which classifier evidence for a particular visual stimulus correlated with behavioral changes on subsequent stimulus presentations. Using a negative priming paradigm, they presented two overlapping stimuli of differing categories (faces, houses, shoes and chairs). Participants were required to pay attention to one of these stimuli, ignoring the other stimulus. In negative priming, an attended stimulus that was ignored in the previous trial typically shows slower reaction times (RTs) compared to novel stimuli. The authors presented evidence for maximal negative priming effects when the unattended stimulus in the previous trial showed moderate levels of excitability (as measured by “evidence” for the stimulus using MVPC) compared to low or high levels. They therefore concluded that moderate (but not low or high) activation of an unattended stimulus results in recognition impairment when that stimulus is subsequently attended. Critically, given their principal concern related to assessing the degree of “evidence” for a specific stimulus category across the whole epoch, they used frequencies from 2 to 128 Hz. Thus frequency selection may have including frequencies relating to slower event-related components (e.g., the N170 face related component). This is entirely appropriate in situations where the principle concern is searching for evidence for the activation of a particular representation, but would not be appropriate for testing physiological mechanisms of memory such as those involving theta-coupled replay.

As illustrated in the study by Newman and Norman (2010), decoding approaches utilizing a broad frequency spectrum for MVPC seem particularly useful to understand representational differences between different types of memory and can reveal

the time when such representations emerge during encoding or retrieval.

5. Future applications

The potential future applications of MVPC of MEG/EEG data in memory research are manifold. For instance, MVPC can be used to understand how memory retrieval based on perceptual or semantic priming, familiarity or recollection, differ in terms of the timing and dynamics of their neural representations. It is potentially useful for tracking memory consolidation, for instance, by recording MEG/EEG during sleep and detecting reactivations of context or item information. Finally, it is feasible that MVPC based decoding can provide new insights into memory deficits in patients with amnesia by revealing which representational aspects of context or item memory fail to be reactivated during retrieval. In the following, we will highlight some examples for future applications in more detail.

As illustrated in Fig. 3, the decoding approach outlined above for working memory maintenance can also be useful to uncover reactivation mechanisms underlying the recollection of past events in episodic memory. One possible approach is to train MVPCs at different time windows (e.g., every 100 ms, depending on the frequency composition of features used for decoding) during encoding. Each of these classifiers is then used independently to classify data from the retrieval phase. For example, a significant classification between two categories (e.g., faces and scenes) may emerge during encoding at ca. 200 ms post stimulus onset. Using MVPCs trained at this time window it is possible to search for reactivation of this face/scene information at retrieval. Such an approach would allow one to assess the time course of memory replay during the retrieval phase and would provide insight as to which types of information from the encoding period are reactivated during retrieval.

As we have tried to highlight in this review, it is possible to place different types of conceptual emphasis on MVPC when investigating such questions, and to focus either more on characterizing representations or on neural dynamics. A hallmark of recollection is that different types of information such as time, location and sensory information need to be bound together despite their likely distribution across disparate brain regions. The widespread interconnections of MTL regions provide support for its role as a convergence zone for such distributed information (e.g., Marr, 1971), and the mechanism of theta-gamma cross-frequency coupling outlined above (e.g., Jones, & Wilson, 2005; Lee, Simpson, Logothetis, & Rainer, 2005; Sirota, et al., 2008) may also enable long-range MTL-neocortical interactions during recollection. Although there is now converging evidence that theta and gamma oscillations (Guderian, & Duzel, 2005; Klimesch et al., 2001; Duzel, Neufang, & Heinze, 2005; Steinvorh, Wang, Ulbert, Schomer, & Halgren, 2010; Sederberg et al., 2007) play a role during recollection, it has so far not been possible to relate these to the neural dynamics of replay of memories during recollection in humans. Using MVPC on MEG/EEG data, it should now be possible to achieve this by restricting MVPC training at encoding to fast oscillations in the beta/gamma range. The timing of replay during retrieval can then be used to test whether beta/gamma related replay incidents are theta-coupled. In contrast, using MVPC with a broad frequency coverage (including also slow frequencies) may be more appropriate to characterize representational differences between different qualities of memory retrieval (e.g., priming, familiarity, recollection). In addition to existing fMRI evidence for memory replay during recollection and familiarity (Johnson, McDuff, Rugg, & Norman, 2009), as well as fMRI evidence for a reactivation of source related representations

during retrieval (McDuff, Frankel, & Norman, 2009), this type of MEG/EEG based decoding can reveal the timing of such process specific reactivations.

A methodologically challenging but promising future application of MVPC on MEG/EEG data could emerge from combining non-invasive whole-head MEG/EEG recordings with intracranial recordings of single unit activity in humans, for instance in patients undergoing presurgical evaluation for pharmaco-resistant epilepsy. MEG is particularly useful in surgical patients because it is contact-free and can therefore be more easily acquired than scalp-EEG. This type of approach would enable us to relate single-unit activity in structures such as the hippocampus to distributed memory reactivation in working memory or episodic memory. In addition to periodic theta-coupled replay, as discussed above, there is another active maintenance mechanism which is persistent neural firing (for reviews see—Miller, & Cohen, 2001; Hasselmo, & Stern, 2006). To what extent the two mechanisms interact with each other is unclear (Lisman, & Idiart, 1995; Mehta, 2005). Although there is physiological evidence that MTL regions surrounding the hippocampus can engage in persistent firing (Egorov, Hamam, Franssen, Hasselmo, & Alonso, 2002) and persistent maintenance (Miller, Li, & Desimone, 1993), there is no clear cut evidence yet for persistent firing during maintenance in the hippocampus (for a discussion of the difference between persistent and periodic firing see Mehta (2005)). Hence, for the time being, there is converging evidence for a hippocampally mediated periodic replay mechanism and no clear evidence for a persistent maintenance mechanism in the hippocampus. Nevertheless, the aforementioned approach (Fig. 3) of temporally decoding encoding events every 60–100 ms is biased towards detecting periodic replay and is therefore unsuited to isolate persistent firing based maintenance. From the vantage point of a hippocampal contribution to replay, this limitation could be overcome by combining widespread cortical recordings of whole-head MEG/EEG data (to enable MVPC based decoding) with direct hippocampal recordings of neural firing.

In terms of future applications in studies of memory processing during encoding, MVPC studies with broad frequency coverage can, for instance, be used to investigate how the nature of representations at encoding relates to the ability to later retrieve these representations. One question is whether the extent to which categories of items encountered during encoding are separated into spatially and spectrally distinct brain activity patterns relates to later episodic memory performance. Using fMRI, Kuhl, Rissman and Wagner (2011) have shown that, during encoding, higher classification accuracy of items belonging to different categories can predict later recollection. Higher classification accuracy during encoding suggests better separation of content representations related to different categories of items and, apparently, this separation aids later retrieval. With EEG/MEG, the findings of Kuhl et al. (2011) can be taken further to determine at which time window during encoding, classification accuracy relates to later memory and by inference, when the content-separation processes that improve episodic memory have occurred. Of note, content-separation as described here and in Kuhl et al. (2011) refers to distinct cortical representations. The hippocampus is also capable of assigning distinct neural representations to stimuli and this process is referred to as pattern-separation (O'Reilly, & McClelland, 1994; Bakker, Kirwan, Miller, & Stark, 2008; Clelland et al., 2009; Norman, 2010). Evidence for hippocampal pattern separation for items that are perceptually similar has been recently observed in the human hippocampus and this is compatible with computational models about hippocampal neuronal populations in dentate gyrus (Bakker, et al., 2008). To what extent cortical content-separation and hippocampal pattern-separation interact remains to be established.

6. Conclusion

The application of MVPC based techniques to MEG/EEG data on memory is still in its infancy. There are a number of methodological issues, some of which were highlighted in this review, that still remain to be appropriately resolved. However, it is already evident that the benefits of MVPC combined with the temporal precision of MEG or EEG are well suited to revealing important new insights into memory function. Using MVPC in conjunction with MEG/EEG allows tracking memory representations in time and relating this timing to ongoing neural dynamics. This enables a more mechanistic investigation of memory functions as has been possible in the past. It is hoped that future research will take advantage of this powerful technique as it provides a means to non-invasively test neurocomputational models of memory and to link insights on memory function gained from studies in rodents and non-human primates with memory function in humans.

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