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A consensus statement: Defining terms for reactivation analysis

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Abstract

During a two-day Royal Society meeting entitled "*Memory reactivation: replaying events past, present and future*" held at Chicheley Hall in May, 2019 we discussed and defined a set of terms for investigating and reporting in memory reactivations to facilitate a common language and thus simplifying comparison of results. Here, we present the results of the discussion and supply a set of terms such as reactivation and replay, for which the authors have reached a common consensus.

Introduction

This special issue of the Philosophical Transactions of the Royal Society focuses upon the topic of memory reactivation and follows a two-day meeting entitled "*Memory reactivation: replaying events past, present and future*" held at Chicheley Hall in May, 2019 (please see Editorial [Robertson & Genzel, 2020]). At the meeting participants met to discuss the definition of terms for investigating and reporting memory reactivations to create a common language to simplify the comparison of results across studies. We summarize the results of these discussions and provide a consensus for the definition of various terms, and how they should be used. We do not intend this to be definitive, or eternal. As the field progresses and more insights are gained, we very much hope that definitions will be refined, clarified, and modified as our understanding of these offline processes advances. We hope that these definitions though provide an important and useful foundation; if only, to bring into sharper focus what remains poorly understood, or frankly unknown.

Replay and reactivation

One key phenomenon in memory research is the observation of experience-based neural activity patterns during prior or subsequent rest, sleep or active periods. This type of brain activity has been recorded across many species from rodents, non-human primates, to humans using a diverse array of techniques from single-unit recording to functional imaging such as, fMRI and MEG/EEG. Across these species and techniques a variety of terms such as replay, reactivation and reinstatement have been used to describe different processes: for example, the re-emergence during offline periods for memory consolidation in contrast to re-emergence during online periods for memory retrieval. Critically, the same terms are often used to describe distinct observations, potentially obscuring fundamental differences in the underlying neuronal or circuit behaviour.

Our discussions lead to a consensus about the definition for a variety of important terms (see Box). Most importantly we suggest that 'reactivation' be the umbrella term describing the re-emergence of a pattern of neuronal activity (in any behavioural state) that represents a prior experience significantly and stronger than the corresponding pattern of activity preceding that experience when novel. The pattern does not have to be established at the individual neuron level but instead can be present in any measuring technique (e.g. individual unit activity with intracranial recordings as well as multi-voxel pattern analysis in fMRI BOLD signal) and validated with variety of analysis methods (e.g. rank order, sequenceless methods, explained variance). We further define 'replay' as a specific form of reactivation containing the same defining criteria above, but adding that it must contain sequential information, e.g. a sequence of place cells or Bayesian decoding of a path. 'Reinstatement' is defined as a reactivation in the wake state and 'retrieval' when reactivation of memory could lead to a behavioural output guided by the reactivated memory trace. Of note, retrieval does not mean that the actual future behaviour has to be reactivated but instead can also be a reactivation of a past experience of negative salience to be avoided in future behaviour.

Preplay and prospective replay

Recently, multiple reports have described patterns of offline activity which correlate with those expressed during a future experience [1-3]. Importantly, however, at least two underlying mechanisms can explain these observations: 1) experience-dependent representations are heavily influenced by pre-existing circuitry, which is revealed during pre-experience offline events; and 2) experience modifies the brain's circuitry to allow prior experiences to be flexibly retrieved and used to guide future behaviours. Strong evidence supporting both explanations has been reported, and these two phenomena might represent or reflect distinct underlying mechanisms. Thus, we suggest to separate these into: (1) preplay, which describes network pre-configurations that cannot be simply explained by documented prior animal experience and that can later be used to map on future experience; and (2) prospective replay, which are temporal sequences within a known environment that occur during behaviour and are thought to be recruited to represent a future action, e.g. planning of a navigational path [4].

Neuronal ensembles, cell assemblies and engrams

Memories are thought to be encoded in a network of neurons and many techniques can be applied to identify such cell groups. However, each technique will measure only certain network properties and thus descriptions and perhaps even differential terminology used should reflect this. We propose that the umbrella term for any identified group of neurons with coordinated activity should be neuronal ensembles, since this is the clearest and most basic description that can be applied to most analysis techniques. The term cell assembly should only be used if it has been shown that the neuronal ensemble shares anatomical and/or functional connections. Neural population would describe larger cell groups. The term engram should be used for cell assemblies coactivated during an animal experience and whose activation is sufficient to recall, in part, that experience.

Describing not interpreting

Finally, we propose that one should return to primarily using terminology and descriptions that incorporates information about the technique used instead of inferring function, especially in short descriptions such as the abstract. For example, one should use correlated fluctuations instead of functional connectivity when describing results from methods such as Granger causality analysis, fMRI resting state analysis, EEG coherence analysis and other cross-spatial time-course analysis.

The same would be true for reactivation analysis-techniques. Diversity of such techniques is increasing and to readers outside the field, it is often not apparent how they are different and how this could influence interpretation. For example, most reactivation studies derive a pattern from specific events during the experience and then search for this pattern in e.g. sleep. However, the one study reporting memory reactivations in REM, derived the pattern from the REM period and searched for it in the wake experience [5]; a critical difference that could affect interpretation and is not apparent to the casual reader. Further, many newer analysis methods are based on unsupervised machine-learning approaches and search for reoccurring patterns during e.g. sleep without deriving a pattern from any wake experience. These differences can be critical when comparing results across experiments and should always be prominently reported.

Summary

We have produced a consensus of how various terms are defined and used. Our hope is that using this, as a guide will foster greater understanding, and appreciation for what insights are being provided within and across studies. Agreeing on to the use of terms such as reactivation, replay, preplay, and prospective replay in a consistent and similar manner across studies, will facilitate comparability within the field and enable understanding beyond our field.

Box – Defining characteristics of memory reactivation

Reactivation: patterns present during learning/encoding are activated again at a later time point stronger than prior to learning/encoding. The pattern does not have to be measured on the individual neuron level but instead can be present in any measuring technique (e.g. by measuring individual unit activity with intracranial recordings as well as multi-voxel pattern analysis in fMRI BOLD signal [6]) or a variety of analysis methods (e.g. pattern matching [7], Bayesian [8] or other decoding, explained variance [9, 10]).

Replay: a specific form of reactivation which includes sequential (temporal and/or spatial) information [11]. The sequence does not have to be a perfect replicate of the original but can contain e.g. less spikes when measured in unit activity or different temporal dynamics as speed-up or stationary moments.

Reinstatement: a reactivation during the wake state e.g. [12]

Retrieval: a reactivation in the wake state that would occur most likely during behaviour and can lead to a behavioural output guided by the previous experience/memory. This is in contrast to reactivations after learning for memory consolidation. e.g. [4]

Consolidation: the offline processing of memories after encoding that leads to lasting changes in network activity patterns to produce behavioural changes such as the stabilization of a memory, its enhancement or reorganization [13].

Prospective Replay: temporal sequences expressed within a known environment that encode information predictive of future behaviour. e.g. [1, 14]

Retrospective Replay: temporal sequences expressed within a known environment that encode information correlated with past behaviour. [11]

Forward Replay: any replay in which the sequential information is expressed in the temporal order of experience. [11, 15]

Reverse Replay: any replay in which the sequential information is expressed in the reverse temporal order of experience. [8, 15, 16]

Preplay: Temporal patterns of activity which are correlated with the patterns that will arise during a future novel experience. [2]

Correlated/coactive neuronal ensembles: a group of cells with coordinated activity (captured by most techniques such as PCA, ICA, unsupervised algorithms, explained variance) e.g. [7]

Neural population: large coactive neuronal ensembles

Cell assembly: anatomically and/or functionally connected neuronal ensemble whose temporal pattern of activity is not simply due to firing rate inhomogeneities across neurons and is not simply driven by external cues.

Engram: cell assembly coactivated during an animal experience and whose activation is sufficient to recall, in part, that experience [17]

Correlated fluctuations: this term should be used instead of functional connectivity to correctly describe the phenomena e.g. resting state analysis

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