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Tracking neural correlates of successful learning over repeated sequence observations

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The neural correlates of memory formation in humans have long been investigated by exposing subjects to diverse material and comparing responses to items later remembered to those forgotten. Tasks requiring memorization of sensory *sequences* afford unique possibilities for linking neural memorization processes to behavior, because, rather than comparing across different items of varying content, each individual item can be examined across the successive learning states of being initially unknown, newly learned, and eventually, fully known. Sequence learning paradigms have not yet been exploited in this way, however. Here, we analyze the event-related potentials of subjects attempting to memorize sequences of visual locations over several blocks of repeated observation, with respect to pre- and post-block recall tests. Over centro-parietal regions, we observed a rapid P300 component superimposed on a broader positivity, which exhibited distinct modulations across learning states that were replicated in two separate experiments. Consistent with its well-known encoding of surprise, the P300 deflection monotonically decreased over blocks as locations became better learned and hence more expected. In contrast, the broader positivity was especially elevated at the point when a given item was newly learned, i.e., started being successfully recalled. These results implicate the Broad Positivity in endogenously-driven, intentional memory formation, whereas the P300, in processing the current stimulus to the degree that it was previously uncertain, indexes the cumulative knowledge thereby gained. The decreasing surprise/P300 effect significantly predicted learning success both across blocks and across subjects. This presents a new, neural-based means to evaluate learning capabilities independent of verbal reports, which could have considerable value in distinguishing genuine learning disabilities from difficulties to communicate the outcomes of learning, or perceptual impairments, in a range of clinical brain disorders.

Introduction

Despite many significant advances, our understanding of the neural mechanisms underlying the commitment of information to memory remains incomplete. While the finer details of the plastic changes underlying memory trace formation are best examined on synaptic and neuronal levels (Kandel and Schwartz, 1982; Martin et al., 2000), lower-resolution human neuroimaging and neurophysiology can offer valuable, complementary insights owing to the feasibility of linking neural signals to complex behaviors that can readily be manipulated and measured. In human studies of memory formation, subsequent-recall reports have been the major behavioral currency, and many fundamental insights have been gained by comparing neural responses to items that were later remembered versus forgotten (Fernandez et al., 1999; Gonsalves and Paller, 2000; Karis et al., 1984; Paller et al., 1987b; Wagner et al., 1999).

In the present study we examine from a new perspective the particular case of memorization of sensory sequences over repeated observations, which naturally provides experimental traction in the study of neural correlates of memory formation in several important ways. First, rather than making comparisons among items that may vary widely in memorability, semantic content, and/or sensory characteristics, comparisons within a sequence can be made among highly simplified tokens which minimize these and other factors known to influence learning success, such as item-to-item interactions (Gobet et al., 2001). Second, states of learning can in fact be compared *within-item* because the exact same stimuli are presented repeatedly over the course of learning, allowing endogenous variance in the efficacy of memory formation across and within subjects to be clearly distinguished from inter-stimulus variability. Third, learning state transitions can be traced gradually, from an individual element being completely unknown, while it is being learned, to being fully committed to memory. This

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gradual aspect is particularly important because it provides the ability to examine the potentially incremental nature of memory formation (Schlaghecken et al., 2000), which cannot be readily done using dichotomous subsequent recall outcomes. Fourth, sequence learning over repeated observations systematically influences stimulus expectancy, thus allowing us to relate these gradual changes in sequence knowledge to stimulus-bound surprise and its established neural correlates (Duncan-Johnson and Donchin, 1977; Kolossa et al., 2012; Mars et al., 2008; Sutton et al., 1965). To realize these advantages in the present study, we examined event-related potentials (ERP) of subjects attempting to memorize sequences of spatial locations – possibly the most elementary type of sensory information – over several blocks of repeated observation, with recall tests before and after each block.

Previous research has successfully employed sequences to shed light on issues related to plasticity in primary sensory areas through learning (e.g. Gavornik and Bear, 2014), differences between explicit and implicit learning (e.g. Aizenstein et al., 2004; Baldwin and Kutas, 1997; Rüsseler et al., 2003), and primacy and recency effects (e.g. Rushby et al., 2002; Wiswede et al., 2007). Some studies have examined spectral changes exhibited after versus before learning (Moisello et al., 2013), or more finely over the course of repeated presentations (Madhaven et al., 2015; Zhuang et al., 1997), in the latter cases linking the changes to motor execution (Zhuang et al., 1997), or memory retrieval (Madhaven et al., 2015) rather than memory formation. To our knowledge, however, no study has yet fully exploited the possibilities outlined above, and tracked neural correlates of memory formation on an element-by-element basis as they develop through discrete learning state transitions.

Neural signal changes that could systematically relate to element-wise learning as well as predict overall learning success can be hypothesized on the basis of two different strands of literature. First, seminal ERP studies of memory found broad, late centro-parietal positivities (300 ms after stimulus onset and onwards) to be increased for items subsequently remembered relative to those forgotten (Karis et al., 1984; Neville et al., 1986; Paller et al., 1987b), which has since been widely replicated in tasks ranging from implicit sequence learning (e.g. Eimer et al., 1996; Schlaghecken et al., 2000) to imagining visual scenes (Gonsalves and Paller, 2000), with greater effects being indicative of stronger memories (Münte et al., 1988; Paller et al., 1988). The same approach has been applied in neuroimaging studies, indicating the involvement of several areas, including left inferior frontal gyrus (De Chastelaine and Rugg, 2014; Kim, 2011; Wong et al., 2013), left fusiform gyrus (De Chastelaine and Rugg, 2014; Kim, 2011), and bilateral hippocampus (Brewer et al., 1998; Kim, 2011; Schendan et al., 2003), in the encoding of memories. There have, however, been indications in functional magnetic resonance imaging (Otten et al., 2001) and electroencephalography (EEG) studies (Paller et al., 1987a; Sanquist et al., 1980; Weyerts et al., 1997) that such neural activation patterns may not be linked primarily to the memorization itself, but more directly to mediating factors such as associative or semantic processing depth, and stimulus complexity (Van Petten and Senkfor, 1996). It is therefore uncertain whether the same subsequent memory effects can be found for simple stimuli inspiring as little associations as the spatial position elements used in the present sequence learning paradigm. Neural correlates of the most basic mechanisms of active memory formation should, in theory, be observed for the learning of information regardless of its semantic content; further, to the extent that their endogenous variation bears on learning efficacy, they should be decreased when learning efforts fail; and finally, assuming they are actively employed specifically for memorization, they should be absent for already well-learned items. A sequence learning paradigm of the kind employed in the present study is uniquely amenable to applying such strong identifying criteria.

A second relevant line of literature concerns the P300 component, a parietal positivity evoked by task relevant stimuli with a peak latency that varies widely (300-1500 ms) as a function of the temporal requirements of stimulus processing (e.g. McCarthy and Donchin, 1988; Twomey et al., 2015). Most important for the current purposes, its amplitude has been found to decrease as a function of subjective stimulus expectancy, or equivalently, increase with stimulus-bound "surprise," across a diverse range of paradigms (Donchin, 1981; Duncan-Johnson and Donchin, 1977; Fu et al., 2013; Horst et al., 1980; Kolossa et al., 2012; Mars et al., 2008; Rüsseler et al., 2003; Schlaghecken et al., 2000; Sutton et al., 1965). In the context of sequence learning, sequence knowledge can be equated to correct stimulus expectancy. Hence, we can hypothesize that P300 amplitude will decrease over the course of learning as sequence knowledge strengthens. More specifically, assuming that increments of sequence knowledge are always gained in varying amounts from one observation to the next, and seldom *lost*, we predict that this P300 decrease will be strictly monotonic. This is distinct from the prediction for signals of active memory trace formation which, as we argued above, will be especially elevated at the point where an element begins to be correctly recalled, stronger than both the preceding and the following sequence observations. Both the abovementioned subsequent memory effects and the P300 tend to be focused at similar centro-parietal topographic sites, which in general complicates their separate measurement. However, the use of the simplest sequence tokens in the present study ensured that stimulus processing was both fast and minimally variable. As a result, the evoked P300 signature was highly transient in the average ERP and could be distinguished to a reasonable degree from less time-restricted processes associated with memory-formation based on temporal scale. We additionally explored the potential for using these neurophysiological components to predict learning success across individuals in a group, as well as across sequence observations within a given individual. Such prediction from electroencephalographic measures alone, independent of behavioral reports, would pave the way towards the development of new diagnostic tools for learning disabilities that involve significant communication difficulties. To facilitate these various analyses, as well as to replicate the principal effects to demonstrate reliability, we analyzed the data of two separate experiments, selectively leveraging variance across and within subjects, respectively.

Materials and methods

Participants

Twenty-one right-handed participants volunteered for Experiment I. One participant was excluded from the analysis because the sequence was memorized perfectly by the end of the first block, and one further participant was excluded due to an excessive number of artifacts (>95% of trials). This yielded a final sample of 19 participants for Experiment I (mean age ± standard deviation = 24.2 ± 4.8 years, 13 male). A different set of six subjects volunteered for Experiment II (mean age ± standard deviation = 22.5 ± 3.67 years, 2 male), with no overlap between the experiments.

All subjects reported normal or corrected-to-normal vision and no current psychiatric diagnosis or history of head injury. All participants gave written informed consent. Procedures were approved by the Institutional Review Boards of the City College of New York and were in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Spatial sequence learning task

In all conditions of both experiments, participants were asked to view a series of identical stimuli presented, one at a time, at a sequence of radial locations. Visual stimuli consisted of filled black circles with a diameter of 1 cm. The set of possible spatial locations lay equidistant around a ring of fixed eccentricity (2 cm; Fig. 1A), and were continuously marked by static circular outlines. Stimuli were presented for