Using event-related potentials to inform the neurocognitive processes underlying knowledge extension through memory integration

Nicole Varga, Emory University
Patricia Bauer, Emory University

Journal Title: Journal of Cognitive Neuroscience
Volume: Volume 29, Number 11
Publisher: Massachusetts Institute of Technology Press (MIT Press): 3 month embargo | 2017-11-01, Pages 1932-1949
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1162/jocn_a_01168
Permanent URL: https://pid.emory.edu/ark:/25593/ts37p

Final published version: http://dx.doi.org/10.1162/jocn_a_01168

Copyright information:
© 2017 Massachusetts Institute of Technology.

Accessed February 26, 2022 12:27 PM EST
Using Event-related Potentials to Inform the Neurocognitive Processes Underlying Knowledge Extension through Memory Integration

Nicole L. Varga and Patricia J. Bauer

Abstract
To build a general knowledge base, it is imperative that individuals acquire, integrate, and further extend knowledge across experiences. For instance, in one episode an individual may learn that George Washington was the first president. In a separate episode they may then learn that Washington was the commander of the Continental Army. Integration of the information in memory may then support self-derivation of the new knowledge that the leader of the Continental Army was also the first president. Despite a considerable amount of fMRI research aimed at further elucidating the neuroanatomical regions supporting this ability, a consensus has yet to be reached with regards to the precise neurocognitive processes involved. In the present research, we capitalized on the high temporal resolution of event-related potentials (ERPs) to inform the time course of processes elicited during successful integration and further extension of new factual knowledge. Adults read novel, related stem facts and were tested for self-derivation of novel integration facts while ERPs were recorded. Consistent with current theoretical models, memory integration was first triggered by novelty detection within 400 msec of experience of a second, related stem fact. Two additional temporally staged encoding processes were then observed interpreted to reflect (1) explicit meaning comprehension and (2) representation of the integrated relation in memory. During the test for self-derivation, a single ERP was elicited, which presumably reflected retrieval and/or recombination of previously integrated knowledge. Together, the present research provides important insight into the time course of neurocognitive processing associated with the formation of a knowledge base.

INTRODUCTION
Semantic memory is a system for representing knowledge accrued across experiences, organizing the information categorically, and providing accessible representational support for all cognitive functions. A key mechanism through which this network of factual information is formed and by which the further extension of existing knowledge is accomplished is memory integration—combination of separate yet related traces of information (Bauer & Varga, 2016; Bauer & San Souci, 2010). In recent years, there has been substantial investigation of the brain areas and networks underlying memory integration, resulting in gains in our understanding of the neural substrates that support this behavior in adults. Specifically, studies employing fMRI have shown that a hippocampal-medial prefrontal circuit is involved (e.g., Zeithamova, Dominick, & Preston, 2012). Yet because fMRI cannot easily distinguish neural events that occur closely together in time, the series of neurocognitive processes responsible for successful knowledge extension is not fully understood. To address this gap, in the current research we capitalized on the temporal resolution of event-related potentials (ERPs) to elucidate the time course of neural processes responsible for integration and further extension of new factual knowledge in adults.

An ongoing debate in the literature concerns whether knowledge extension through memory integration is achieved through one or multiple mechanisms, as well as whether these mechanisms occur during initial learning, while making inferential judgments, or across both learning and test (see Zeithamova, Schlichting, & Preston, 2012, for a review). One commonly employed approach to assessing memory integration involves training individuals to associate temporally distributed yet arbitrary stimulus pairs (e.g., AB: Chair & Zucchini; BC: Zucchini & Blender) to infer a novel, indirect relation (e.g., AC: Chair & Blender; Schlichting, Zeithamova, & Preston, 2014; Zeithamova, Dominick, et al., 2012; Zeithamova & Preston, 2010). Success is typically measured through a forced-choice transfer test, which requires integration of previously learned information in response to a specific inferential cue (e.g., AC: Chair = Blender or House?). Using this and other paradigms, some studies have demonstrated that hippocampal activation during encoding is predictive of later inference success, in the absence of evidence for the recruitment of additional (Shohamy & Wagner, 2008)
or unique (Schlichting et al., 2014) patterns of activation at the time of test. Conversely, others have shown that integration of a related event is associated with increased activation in the medial temporal lobe during encoding (including hippocampus and parahippocampal cortex); inference at test is then further supported by medial temporal lobe–pFC coupling (e.g., Zeithamova & Preston, 2010). As this mixed pattern of results demonstrates, evidence for both integrative encoding activation and test-induced inferential retrieval activation has been documented in the literature. Yet these seemingly contradictory frameworks are not mutually exclusive. That is, as suggested by Zeithamova, Schlichting, et al. (2012), the relative contributions of encoding and retrieval mechanisms might instead be determined by particular task demands. Examination of how these mechanisms operate under a different set of task conditions, in which the target of learning is factual knowledge as opposed to arbitrary associations, will thus provide important insight into the nature of the process(es) involved.

To further our understanding of memory integration processes, in the present research, we examined how integration operates in real time. The method adopted in the present research was developed in response to the growing need to examine the acquisition of real-world factual knowledge and to mirror everyday learning conditions. Inspired by a paradigm employed by Bauer and Jackson (2015), individuals were taught pairs of true but novel “stem” facts that were related to one another (Stem 1: Apple seeds are called pips; Stem 2: Cyanide is found in pips). They later were tested for self-derivation of new knowledge through integration of the target information (Apple seeds contain cyanide). Compared with paradigms using arbitrary stimuli, this approach has the added value of being about real-world information and, thus, is directly relevant to the issue of how semantic knowledge is built over time. Indeed, consistent with the proposal that memory integration supports the organization of knowledge within long-term memory (e.g., Preston & Eichenbaum, 2013), prior research employing this paradigm provides evidence that integrated knowledge is retained over time, at least over a period of 1 week (Varga & Bauer, 2017), even in 4- and 6-year-old children (Varga, Stewart, & Bauer, 2016; Varga & Bauer, 2013). In light of these findings, in the present research we combined the paradigm with electroencephalographic recordings. ERPs provide a complementary level of analysis that affords millisecond-level temporal resolution, thus offering clarity on the time course of component processes involved as well as key insight into the temporal sequence of neural activation observed during initial encoding and subsequent test for knowledge extension.

Current theoretical accounts of the processes involved in flexible knowledge extension share one feature: They agree that memory integration is invoked under conditions that permit pattern completion, in which exposure to a novel item results in reactivation of memories for prior episodes (Zeithamova, Dominick, et al., 2012). To continue with the previous example, to successfully integrate two novel facts (AB: Apple seeds are called pips; BC: Cyanide is found in pips), the initially learned factual information (AB) must be reactivated while processing the second, related fact (BC), and the shared meaning between them must be bound in memory (ABC). Support for this argument comes from a noteworthy study in which Zeithamova, Dominick, et al. (2012) presented participants with object–scene paired associates and used multivoxel pattern analysis to determine if simultaneous processing of prior objects (AB) occurred upon exposure to novel, related scenes (BC), and vice versa. They found that reactivation of prior, overlapping episodes occurs upon experience of related content and that greater reactivation during initial learning was correlated with transfer success in a later inference test. This finding suggests that memory integration is accomplished through retrieval of prior memory representations. Yet as outlined below, the low temporal resolution of fMRI leaves open the questions of the events that trigger memory integration initially, how quickly integration occurs, and whether it consists of a single or multiple temporally staged processes.

Prevailing theoretical accounts additionally posit that knowledge extension through retrieval-mediated integration is set into motion for the purpose of resolving a detected “mismatch” between newly and previously learned information (Preston & Eichenbaum, 2013; Shohamy & Wagner, 2008). By this logic, one’s current knowledge about pips (that they are equivalent to apple seeds) is reactivated and challenged when an individual newly learns that pips are also associated with cyanide, thus violating memory-based predictions about the semantic meaning one expects to be associated with pips. Support for this argument comes from the finding that during encoding of a related paired associate (BC) the only region in which activity was predictive of success on subsequent inferential judgments was hippocampal subfield CA1, a region thought to play a role in novelty detection (Schlichting et al., 2014). The proposal is that CA1 serves as a comparator that triggers a cascade of subsequent processes required to resolve, integrate, and extend the new knowledge.

In the present research, we tested the hypothesis implicated by patterns of fMRI activity, namely, that multiple subprocesses are involved in integration and extension of new relational knowledge, beginning with novelty detection. Because ERPs provide a continuous measure of processing in real time, they are ideally suited for examination of the component processes underlying successful knowledge extension. We capitalized on the strength of the difference-centered ERP approach, whereby ERPs are quantified based on the time points at which waveforms diverge between experimental conditions (see Voss & Paller, 2008). Specifically, we recorded ERPs during encoding of separate, related facts as well as during
self-derivation of new knowledge at the time of test and subsequently sorted the trials based on whether knowledge extension through integration was successful. Direct observation of differential processing at specific latency intervals will shed light on the processes involved and does not rely on eliciting specific ERP components per se. Nevertheless, valid conclusions are contingent upon whether the ERPs observed exhibit correspondence to ERP components previously identified in the literature (Voss & Paller, 2008). Critically, two well-established ERP components have been shown to reflect the “reactivation” and “novelty detection” operations implicated by fMRI, thereby enabling examination of whether these processes trigger memory integration.

An ERP component that shows sensitivity to novelty detection and that may conceivably reflect reactivation of previously acquired information is the midfrontal old–new effect—a change in neural activity 300–600 msec after stimulus onset over the frontocentral scalp region (reviewed in Wilding & Ranganath, 2012). Systematic reductions in a negative-going voltage fluctuation as a function of repeated exposure to previously viewed items have been reported in several experiments and are argued to reflect facilitated retrieval of stored memories associated with a stimulus (e.g., Eimer, 2000; Friedman & Johnson, 2000). For instance, when a pair of previously presented words is repeated, a less negative-going deflection is observed beginning at 400 msec relative to novel words (Rugg, Doyle, & Holdstock, 1994; Experiment 1). Relevant to the present research, when a word from a previously presented pair is subsequently presented with a new word, ERPs do not exhibit this reduced negativity, presumably reflecting novelty detection and the associated difficulty of processing the current input with respect to the reactivated, prior representation (Rugg et al., 1994; Experiment 3). Importantly, ERPs to repeated items incorrectly judged as “new” also fail to elicit the reduced negative-going deflection typically observed for “old” items, indicating that the midfrontal old–new response is modulated by successful retrieval of prior information (Tsvilis, Otten, & Rugg, 2001). As such, for successfully integrated facts, reactivation of prior knowledge and detection that it differs from new information might be indexed by a more negative going ERP at 400 msec relative to unsuccessfully integrated facts.

Another component that is sensitive to mismatches between current input and prior, related knowledge is the N400—a negative-going fluctuation that reaches maximum amplitude between 350 and 500 msec over the centroparietal scalp region (Kutas & Federmeier, 2011; Federmeier & Laszlo, 2009). A large literature suggests that the N400 amplitude is modulated by expectancy, as measured by cloze probability—the percentage of people who would continue a sentence fragment with the target word—with more negative amplitudes indicative of greater incongruence between current input and memory-based predictions (e.g., Kutas & Federmeier, 2000; Federmeier & Kutas, 1999). For instance, when individuals are presented with sentences that end either in an expected exemplar (“The gardener really impressed his wife on Valentine’s day. To surprise her, he secretly grew some roses.”) or an unexpected exemplar from the same expected category (tulips), the unexpected, within-category violation produces a more negative N400 response by as early as 375 msec (Federmeier & Kutas, 1999). This suggests that semantic memory serves to increase the availability of specific knowledge (by generating memory-based predictions), which impacts semantic processing between 400 and 600 msec. Thus, if integration of separate, related semantic facts is triggered by violation of a memory-based prediction, we would expect to see a similar negative response on successful compared with unsuccessful trials.

As alluded to above, whether additional processes are recruited following novelty detection and the precise nature of the neural activation at the time of explicit testing are not well understood, though it has been proposed that reinstatement, recombination, organization, and/or some form of conflict resolution might be engaged. For instance, a gradual shift from hippocampal to ventromedial prefrontal cortex activity has been observed when participants are exposed to the same paired associates repeatedly at encoding (e.g., Zeithamova, Dominick, et al., 2012), suggesting that the ventromedial prefrontal cortex is recruited after initial integration and thus might index explicit recombination of the relations (e.g., Zeithamova & Preston, 2010) and/or organization of integrated knowledge in long-term memory (e.g., Hasselmo & Eichenbaum, 2005). In contrast, because the same pattern of hippocampal activity elicited at encoding is reinstated when a successful inference is made, previously integrated representations might be directly retrieved during the test for knowledge transfer (Schlichting et al., 2014). An additional ERP component that may reflect successful “integration” or “recombination” of separate stem facts in memory is the P600 or Late Positive Component (LPC)—positive neural activity beginning around 500 msec and continuing until approximately 900 msec over central-parietal scalp regions. This component has been linked to extracting and representing relational meaning in memory (e.g., Bauer & Jackson, 2015).

Finally, because we expected differences in ERPs reflective of reactivation/novelty detection and relational binding/recombination, we also took extra steps to constrain our interpretation of the cognitive processes indexed by the ERPs. That is, we examined relations between the ERPs and six standardized cognitive operations: long-term storage and retrieval, novelty detection/semantic prediction, semantic comprehension, relational abstraction, working memory, and STM. Together, the approach provides a framework from which to understand how the neurocognitive processes underlying memory integration unfold in real time.
METHODS

Participants

A total of 120 adults participated. The sample consisted of individuals whose electroencephalographic data were collected as part of a larger study (Varga & Bauer, 2017), the results of which were not included in any prior published reports. All participants were native English speakers enrolled in psychology courses at a select private university. Because the goal of the investigation was to inform the neurocognitive processes involved in successful (vs. unsuccessful) knowledge extension through memory integration, data are reported for participants in the middle of the performance distribution, who contributed comparable levels of successful and unsuccessful trials. Of the 120 individuals tested, 58 satisfied our inclusion criteria of a minimum of 10 successful and successful trials. Of the 120 individuals tested, 58 satisfied the results of which were not included in any prior published reports. All participants were native English speakers enrolled in psychology courses at a select private university. Because the goal of the investigation was to inform the neurocognitive processes involved in successful (vs. unsuccessful) knowledge extension through memory integration, data are reported for participants in the middle of the performance distribution, who contributed comparable levels of successful and unsuccessful trials. Of the 120 individuals tested, 58 satisfied our inclusion criteria of a minimum of 10 successful and successful trials. Of the 120 individuals tested, 58 satisfied

encoding

Stimuli

The stimuli were 60 stem facts and 30 novel integration facts. Facts ranged from 4 to 10 words and were intended to be educationally meaningful. For instance, two stem facts about art history were A popular sculpture made from a urinal is called Fountain (Stem 1) and Duchamp's most well-known work is named Fountain (Stem 2). Integration of the stem facts could lend itself to derivation of a novel integration fact: Duchamp's most popular work consisted of a urinal (Self-derived Fact). The stimuli captured a variety of logical relations regularly encountered in everyday learning conditions and which have previously been shown to invoke integration mechanisms (Zeithamova, Schlichting, et al., 2012). Importantly, prior research has shown that the facts are novel to adults and that exposure to both facts from a given pair is necessary for derivation of the novel integration fact (see Varga & Bauer, 2017; Experiment 1). Specifically, when participants were exposed to only one of the two stem facts from a pair, they self-derived the novel integration facts only 11% of the time, which significantly differed from the 44% demonstrated when both stem facts were provided. Moreover, with the exception of one fact pair, for all fact pairs included in the stimulus set, self-derivation was at least twice as great in the 2-stem condition than the 1-stem condition. In the case of the one exception, self-derivation was nearly identical in the 1-stem and 2-stem conditions. As a result, trials assessing performance on this fact were excluded from all reported analyses (see Varga & Bauer, 2017).

Procedure

The procedure involved three phases: encoding, test, and cognitive assessments.

Encoding

Participants were told we were interested in whether neural activity for newly learned information differs as a function of subject domain. They were fitted with a Brain Products high-precision ActiCAP (ActiCAP GmbH, Munich, Germany) with 32 electrodes positioned according to an adaptation of the International 10–20 system (Jasper, 1958). Once electrode impedances were lowered, participants read 60 sentences on an LCD computer monitor. As depicted in Figure 1A and B, words of the sentences were presented one at a time for 400 msec each. ERPs were time-locked to a sentence-final target word, which consisted of a repeated word linking related stem facts to one another (e.g., Pips, Fountain). Following each sentence, participants were shown a decision screen and asked to indicate, via a button-press response, whether the information conveyed was novel or known. The incidental task was designed to ensure that participants attended to the facts while also corroborating the pretext of the study purpose (i.e., learning of novel information across subject domains). At no time were participants informed that any of the sentences was related. Across the encoding phase, paired stem facts were separated by a lag of two to four intervening sentences, thereby creating temporal distance. Moreover, the short lag served to promote recognition of the relatedness between paired facts, thereby allowing for examination of memory integration under optimal conditions. Fact order was counterbalanced such that each stem fact from a pair was presented in the first or second serial position an approximately equal number of times across the sample.

Test

After a 5–10 min buffer activity, participants were presented with 30 sentences conveying facts derived through integration of the previously presented stem facts. As depicted in Figure 1C, the sentences were presented in the form of questions by replacing the final word of each fact with “?” ERPs were time-locked to the onset of the “?”, which cued participants to generate a one-word answer that could accurately complete the sentence. Participants were given an unlimited amount of time to think of a response. When
an answer was generated, they made a button-press response which was followed by an “Answer” screen signaling them to speak the answer aloud. To preclude speaking during the recording epoch, responses logged before 2400 msec after onset of the “?” did not initiate an “Answer” screen. Responses were required on all trials. Some fact pairs could elicit an accurate response derived from the stem facts but that did not necessitate integration of them. In these situations, a disambiguating follow-up question was asked (e.g., Can you tell me another word that would also accurately complete this sentence?). Once an answer was provided, the participant was instructed to remain still and alert. When the speaking-related muscle activity returned to baseline (after about 10–30 sec), the experimenter initiated the next question.

Cognitive Assessments

Participants returned to the laboratory approximately 1 week later (M delay = 7.08, SD = 0.76, range = 6–11 days). The Woodcock Johnson Test of Cognitive Abilities, Third Edition (Woodcock, McGrew, & Mather, 2001), the Test of Memory and Learning, Second Edition (Reynolds & Voress, 2007), and the Woodcock Language Proficiency Battery-Revised (Woodcock, 1991) were used to assess six standardized cognitive domains (see Table 1 for description of each task). To avoid the potential for unique order effects, cognitive assessments were administered in the following fixed order: (1) Digits Forward, (2) Concept Formation, (3) Digits Backward, (4) Visual-Auditory Learning, (5) Passage Comprehension, and (6) Verbal Comprehension.

Electrophysiological Recording and Data Reduction

Brain electrical activity measured at Session 1 was recorded at 32 sites using active Ag/AgCl electrodes mounted in an elastic cap (ActiCAP GmbH). Application and recording
were conducted while participants were seated 90 cm in front of the monitor. Reference electrodes were mounted to the left and right mastoids via double adhesives. Impedances were consistently below 35 kΩ and generally below 15 kΩ. The EEG was continuously sampled at 500 Hz for offline analysis using open-source Pycorder software (Brain Products, Gilching, Germany). Data were referenced online to a virtual ground. No band-pass filters were applied during data acquisition.

Offline data processing was completed using EEGLAB 13.4.3b (Delorme & Makeig, 2004) and ERPLAB 4.0.3.1 (www.erplab.org) operating in Matlab R2014a (MathWorks, Natick, MA). A high-pass filter with a half-amplitude cutoff of 0.1 Hz and a roll-off of 12 decibels/octave was first applied to the raw EEG signal. Data then were processed with independent component analysis to identify and remove artifacts caused by eyeblinks, saccades, line noise, and bursts of EMG. Following independent component analysis, a low-pass filter with a half-amplitude cutoff of 30 Hz and a roll-off of 12 decibels/octave was applied, and data were subsequently re-referenced to mathematically linked mastoids. The continuous EEG data for each participant was segmented into 2600 msec epochs beginning 200 msec before stimulus onset and ending 2400 msec after stimulus onset. The 200 msec prestimulus window was used to correct for baseline activity on each individual trial, and trials containing amplitudes that exceeded ±150 μV were rejected from the averaged epochs. Across participants, we created separate grand averages for trials in the Stem 1 (Encoding), Stem 2 (Encoding), and Self-derivation (Test) conditions, which were each further sorted trial-by-trial according to self-derivation performance (correct vs. incorrect). Average trial counts for each condition of interest are provided in Table 2.

### Data Analysis

Several key assumptions guided our analysis of the ERP data. First, if new knowledge is integrated with existing knowledge at the time of encoding, it is necessarily the case that memory integration occurs upon encoding of the second, related stem fact (as opposed to encoding of the first stem fact from a target pair). Therefore, we hypothesized that integration would be set into motion upon exposure to the Stem 2 fact and that differences in neural processing of Stem 2 as a function of subsequent performance would reflect the processes involved in memory integration. Second, because each Stem 2 fact was time-locked to a repeated word (Pips, Fountain, etc.) which served as a relational link to previously learned factual content (first presentation of Pips, Fountain, etc. in Stem 1), the Stem 1 and Stem 2 conditions should naturally give rise to different levels of repetition and thereby familiarity. To control for this feature and increase power, the primary encoding analyses separately examined time points in which ERP responses within the Stem 1 condition and within the Stem 2 condition differed as a function of performance. Third, if integration is triggered by the elicitation of associative novelty signals (Schlichting et al., 2014; Shohamy & Wagner, 2008), then a more negative-going ERP should be observed between 400 and 600 msec during encoding of Stem 2 facts, whereas Stem 1 processing should not differ as a function of performance as relational comparison is not yet possible.
As discussed previously, novelty detection is speculated to trigger a host of subsequent processes required to integrate conflicting information in memory (Schlichting et al., 2014). Moreover, ERP effects are typically observed across multiple electrodes and persist for tens of hundreds of milliseconds (Maris & Oostenveld, 2007). Thus, to detect reliable ERP performance differences at encoding and test phase latency intervals in which we did not have a priori hypotheses, we conducted a series of mass univariate analyses in which t tests were performed for all time points, scalp locations, and experimental conditions while correcting for multiple comparisons. A cluster-based permutation approach was used in particular because it has been shown to be the most powerful mass univariate procedure for detecting broadly distributed ERP effects (Groppe, Urbach, & Kutas, 2011a, 2011b; Maris & Oostenveld, 2007). The analyses were conducted in two parts: (1) Single-channel analyses: We first sought to determine whether, at each individual electrode, clusters of adjacent time samples exhibited a similar difference in amplitude (in sign and magnitude) between correct and incorrect trials within each experimental condition (Stem 1, Stem 2, Test). (2) Multichannel analyses: We evaluated whether the ERP differences observed between correct and incorrect trials at prior, single-channel latencies were statistically significant in spatially adjacent electrode clusters. Because the neurocognitive processes involved in memory integration are supported by a distributed hippocampal-medial prefrontal network (Zeithamova, Dominick, et al., 2012), we expected to see spatiotemporally distributed effects.

A priori Analyses

Because functionally and temporally similar novelty effects have been shown to be maximal between 400 and 600 msec at frontal midline and frontocentral scalp sites for recognition memory (e.g., Wilding & Ranganath, 2012) and at centrotemporal scalp sites in linguistic paradigms (e.g., Federmeier & Kutas, 1999), we focused the analysis on an electrode cluster that spanned these topographical regions (Pz, F3, Fz, FC1, FC2, Cz, C3, C4, CP1, and CP2; see Figure 2 in gray). For each condition (Stem 1, Stem 2), mean amplitude of the ERP response was examined via a two-way repeated-measures ANOVA with factors of Performance (correct or incorrect) and Electrode site. Greenhouse–Geisser corrections were applied in cases of violation of sphericity. Because they do not inform the research question, effects of Electrode site were not reported unless they interacted with Performance.

Single-channel Cluster Analyses

The analyses focused on all time samples between 150 and 2400 msec (1125 total time points). Within each experimental condition, the ERPs to correct and incorrect trials were submitted to repeated-measures, two-tailed permutation tests based on the cluster mass statistic (Bullmore et al., 1999). That is, each participant’s ERP data (within experimental conditions) was randomly partitioned 2500 times into correct and incorrect performance bins. For the real data and for each random within-participant permutation, the ERP amplitude between correct and incorrect trials was compared via repeated-measures t tests. All time samples with a t value corresponding to an uncorrected p value of .05 or less were formed into clusters that included any temporally adjacent significant t values with the same sign (positive or negative). The “mass” of each cluster was then calculated by summing the t scores across time samples forming the cluster, and the most extreme cluster mass in each of the 2501 sets of t tests was used to generate a null distribution. Finally, the p value of the observed difference was derived by calculating the proportion of random partitions that resulted in a larger t value than the observed effect. Because the null distribution was derived by taking the maximum cluster-level statistic across all time samples, this procedure controlled for the familywise error rate across time samples. It also reduced sensitivity to detecting smaller clusters, which is why this technique is recommended as a complement rather than a replacement for a priori analyses. This procedure was conducted separately for all 30 nonmastoid channels. If
similar performance differences at overlapping latencies were observed for at least two channels, the mean onset and offset latencies across electrode sites were submitted to the multichannel analyses. This second step was taken for all analyses in which reliable performance-related single-channel patterns of temporal activity were initially detected, thereby enabling test of whether these channels formed significant spatiotemporal clusters across distributed regions of the scalp.

Multichannel Cluster Analyses

Cluster-based multichannel analyses were conducted in the same manner as the single-channel analyses with two key exceptions. First, instead of examining all time samples between 150 and 2400 msec, separate repeated-measures, two-tailed permutation tests were conducted only for the latency intervals identified by the single-channel latency analyses (i.e., Stem 1: 1183–1349; Stem 2: 1147–1297 and 1453–1647; Test: 1173–1357). Second, instead of clustering the data per temporal adjacency alone, the ERPs to correct and incorrect trials were formed into clusters on the basis of both temporal and spatial adjacency. That is, channels within approximately 6.08 cm of one another were considered spatial neighbors ($M$ number neighbors per channel = 4.10, $SD =$ 0.90, range = 2–5). As depicted in Figure 2 (thick black lines), this criterion was chosen because it enabled inclusion of all 30 nonmastoid channels into analyses and maximized the number of connections considered between frontopolar and other sites. As in the single-channel analyses, for each of the 2500 within-participant permutations, all $t$ scores corresponding to uncorrected $p$ values of .05 or less were formed into spatiotemporal clusters and the most extreme cluster mass between the permutations and the observed data was used to evaluate the significance of the clusters.

RESULTS

Because only individuals who contributed at least 10 correct and 10 incorrect trials were included in analyses, on
average, participants self-derived the novel integration fact on 51% (SD = 9.69%) of the trials, with performance ranging from 34% to 66%. Figures 3 and 4 depict grand-averaged waveforms for all electrode channels during the encoding and test phases, respectively. Results are divided into four sections: a priori encoding analyses, cluster-based encoding analyses, cluster-based test analyses, and associations between ERPs and cognitive assessments.

A priori Encoding Analyses (400–600 msec)

Grand-averaged waveforms for the a priori electrode cluster and an additional posterior cluster (for comparison) are plotted in Figure 5A and B, respectively. The patterns were consistent with our predictions. That is, as reflected in Figure 5A, no main effect of Performance was observed for the Stem 1 facts, $F(1, 50) = 0.89, p = .35, \eta^2 = .89$. In contrast, a main effect of Performance was observed for processing of the Stem 2 facts, $F(1, 50) = 4.53, p = .04, \eta^2 = .83$, such that ERP responses were more negative on correct trials compared with incorrect trials.

Cluster-based Encoding Analyses

Stem 1 Effects

Single-channel repeated-measures comparisons of the ERPs to correct and incorrect trials (correct-incorrect amplitude difference score) revealed significant positive differences at FP1, FP2, Fz, F3, F4, FC1, FC2, FC5, FC6, C3, C4, CP2, and CP6 in an overlapping latency window from 1172 to 1450 msec across all 13 channels ($M$ latency window = 1183–1349). As depicted in Figure 3 (and Figure 5A though not at the same electrode sites), this cluster constituted a greater relative negativity for incorrect versus correct trials. Moreover, as depicted in the raster diagram in Figure 6A, multichannel cluster analyses on all time points from 1183 to 1349 msec (2521 total comparisons) revealed one significant broadly distributed positive cluster.

Stem 2 Effects

Single-channel repeated-measures analyses of correct–incorrect amplitude difference scores revealed significant positive differences at four channels: FC5, CP6, T7, and

Figure 4. Grand-averaged ERP waveforms across all scalp sites during self-derivation of the integration facts at the test phase. For presentation purposes, the data plotted were down-sampled to smooth the waveforms.
T8 in a latency window ranging from 1122 to 1342 msec across the channels (M latency window = 1147–1297). As reflected in Figure 3 (and Figure 5A though not at the same sites), consistent with the Stem 1 effects (above), this cluster constituted a greater relative negativity for incorrect versus correct trials. The difference observed was slightly earlier than the Stem 1 window reported above yet overlapped with it. As depicted in the raster diagram in Figure 6B, multichannel cluster analyses revealed one significant positive cluster most prominently evident at FC5, FC1, FC1, C3, T7, T8, and CP6 (and less distributed than that observed for Stem 1).

In addition to the significant positive cluster observed from 1147–1297 msec, single-channel analyses also revealed significant negative differences at posterior channels CP1, CP2, CP5, Pz, P3/P4, P7/P8, Oz, and O1/O2 in a latency window from 1424 to 1706 msec (M latency window = 1453–1647). As reflected in Figures 3 and 5B (same electrodes), this significant negative cluster constituted a greater relative positivity for incorrect versus correct trials. As depicted in the raster diagram in Figure 7A, multichannel analyses (2940 comparisons) revealed one significant negative cluster spanning centroparietal, parietal, and occipital sites.

**Cluster-based Test Phase Analyses**

Single-channel repeated-measures comparisons of correct–incorrect ERP amplitude difference scores revealed significant negative differences at all electrode channels except F8, FT10, and T8 in a latency window from 1104 to 1468 msec across all channels (M latency window = 1173–1357). As reflected in Figure 4 (and Figure 8A and B though not the same sites), this broadly distributed cluster constituted a greater relative positivity for incorrect versus correct test trials. Moreover, as depicted in the raster diagram in Figure 7B, multichannel analyses from 1173 to 1357 msec (2790 total comparisons) revealed one significant negative cluster, which was broadly evident across the frontal, central, and posterior scalp regions.
Associations among ERP Responses and Cognitive Assessments

To elucidate the cognitive indices reflected by the ERPs, we assessed between-subject associations among ERP responses and six standardized cognitive measures (see Table 1). We focused on ERPs elicited on both successful and unsuccessful trials. Specifically, we analyzed mean amplitude of the Stem 1 and Stem 2 responses at latency windows in which performance differences were observed during encoding (400–600 msec, 1183–1349 msec, 1147–1297 msec, 1453–1647 msec) as well as responses at test (1173–1357 msec). Guided by the similar negative posterior-maximal clusters observed for Stem 2 ERP responses during the latest encoding window (1453–1647 msec) and the test phase (1173–1557 msec), we further explored whether these encoding (Stem 1 and Stem 2) and test responses were positively associated. Because the \( p \) value of each significant multichannel cluster was assigned to each channel in the topographical array, it is not necessarily the case that every channel in the cluster exhibited an uncorrected \( p \) value of .05 or less. As such, for all correlation analyses, we examined only those channels that exhibited a significant Performance effect in the single-channel analyses. In cases in which standardized measures were missing for some participants, degrees of freedom were adjusted accordingly.

Figure 6. Raster diagrams depicting the second temporally staged encoding effect identified through multichannel cluster-based analyses. Positive Stem 1 (A) and Stem 2 clusters (B) were observed between 1182–1348 msec and 1146–1296 msec, respectively. Each box depicts the result of a \( t \) test at one time sample and one electrode channel. Red boxes indicate channels and time samples in which the Stem 1 correct–incorrect amplitude difference wave was significantly positive.
Of primary interest, ERP responses on correct Stem 2 trials in the a priori 400–600 msec window were positively associated with Concept Formation, \( r(49) = .49, p < .001 \), and Passage Comprehension, \( r(51) = .35, p = .01 \) (Figure 9). ERP responses to Stem 1 (400–600 msec) were negatively associated with Digits Forward on correct trials, \( r(48) = -.29, p = .04 \), and incorrect trials, \( r(48) = -.30, p = .03 \) (Figure 10). ERP responses to Stem 1 (400–600 msec) were also negatively associated with Digits Backward on incorrect trials, \( r(49) = -.32, p = .02 \) (Figure 10). ERP responses during successful self-derivation (1173–1357 msec) were positively associated with Concept Formation, \( r(45) = .31, p = .04 \), and though the effect failed to reach significance, also with Verbal Comprehension, \( r(44) = .27, p = .07 \) (Figure 11). Finally, ERP responses to correct Stem 2 (1453–1647 msec) and correct test responses were correlated, \( r(44) = .32, p = .03 \) (Figure 12). No relations between encoding and test were evident for Stem 1 or incorrect trials.

**DISCUSSION**

The present research afforded elucidation of the temporally staged processes required to successfully extend
knowledge through memory integration. Processing that indexed memory integration was evident by as early as 400–600 msec after the onset of a second, related stem fact. This early effect served as a precursor to subsequent encoding processes recruited between 1147–1297 msec and 1453–1647 msec. Unlike the multiple processes observed at encoding, only one component was sensitive to successful self-derivation of new knowledge at the time of test (1173–1357 msec). Importantly, several of the components shown to distinguish successful from unsuccessful knowledge extension through integration in the present research exhibit the same timing and topography as well-established ERPs documented in the memory literature. Thus, in the discussion to follow, we provide an interpretation of the processes likely reflected by each neural component elicited and discuss how this pattern of results contributes to our theoretical understanding of the nature and time course of successful memory integration.

Detection of a Semantic Deviation Initiates Memory Integration

When participants were presented with a novel fact (i.e., Stem 2) that was related to a previous fact (i.e., Stem 1), information they failed to integrate (as suggested by unsuccessful self-derivation) elicited a more positive ERP deflection than successfully integrated information. The effect was observed between 400 and 600 msec at frontocentral and centroparietal sites. Critically, no differences were observed during the same latency window for novel facts that could not be integrated (i.e., Stem 1 facts for correct vs. incorrect trials). This difference is both temporally and topographically similar to the midfrontal old–new effect (Wilding & Ranganath, 2012; Curran, Tepe, & Piatt, 2006; Rugg et al., 1998, for review). As discussed previously, this component is elicited when participants accurately judge previously studied items as “old” and unstudied items as “new,” with a more
positive-going ERP deflection in response to old items. Consistent with the present results, Curran and Cleary (2003) showed that ERPs on false alarm trials (i.e., mirror reversals of previously studied pictures judged as old) were more positive than those on correct rejection trials. Similarly, in the present research, the more positive-going midfrontal old–new effect was apparent on incorrect, but not correct, Stem 2 trials (e.g., at the second

![Figure 9](image_url)

**Figure 9.** Scatter plots depicting the association between mean amplitude of the ERP response on correct Stem 2 trials in the earliest observed encoding window (400–600 msec) and standardized measures of Passage Comprehension (A) and Concept Formation (B). Passage Comprehension, which measured comprehension of meaning in context based on the predictive nature of Cloze probability, was moderately associated with the “novelty detection” ERP response, \( r(51) = .35, p = .01 \) (A). The association between Concept Formation, which assessed the ability to form and abstract novel relational understandings, and this earliest ERP response was moderate to strong, \( r(49) = .49, p < .001 \). Shaded regions reflect 95% confidence intervals.

![Figure 10](image_url)

**Figure 10.** Scatter plots depicting the association between mean amplitude of the ERP response on correct Stem 1 trials in the earliest observed encoding window (400–600 msec) and Digits Forward (A). Scatter plots depicting the association between mean amplitude of the ERP response on Stem 1 trials that were incorrect (400–600 msec) and Digits Forward (B) and Digits Forward (C) are also presented. ERP responses to Stem 1 facts were negatively associated with STM span regardless of whether self-derivation of the novel integration facts was subsequently correct, \( r(48) = −.29, p = .04 \) (A), or incorrect, \( r(48) = −.30, p = .03 \) (B). Moreover, ERP responses to Stem 1 facts were moderately negatively associated with working memory span, but only on incorrect trials, \( r(49) = −.32, p = .02 \) (C). Shaded regions reflect 95% confidence intervals.
It is therefore plausible that the failure to integrate was linked with the tendency to treat novel but related information as "old" (i.e., to be "lured" into treating new information as if it were simply repeated or old information).

If reliance on familiarity-based processing leads one to mistakenly identify novel yet related information as old, then we must characterize the alternative process that enables recognition of novel but related information as new, ultimately resulting in successful self-derivation. Although the midfrontal old–new effect is most commonly argued to reflect familiarity (Curran et al., 2006; Rugg et al., 1998), others have argued that it reflects conceptual priming and should be interpreted with respect to its precursor, the N400 (e.g., Paller, Voss, & Boehm, 2007). Indeed, because of the temporal overlap between the midfrontal old–new effect and the semantically related N400, some have coined it the familiarity-related N400 (FN400; Curran, 2000). Others suggest that semantic priming (i.e., as indexed by the N400) simultaneously drives familiarity-based old/new judgments with respect to its precursor, the N400 (e.g., Paller, Voss, & Boehm, 2007). Indeed, because of the temporal overlap between the midfrontal old–new effect and the semantically related N400, some have coined it the familiarity-related N400 (FN400; Curran, 2000). Others suggest that semantic priming (i.e., as indexed by the N400) simultaneously drives familiarity-based old/new judgments (Wilding & Ranganath, 2012; Yonelinas, 2002). Consistent with these proposals, in the present research, a more negative-going response was apparent on correct Stem 2 trials for both frontal (FN400; Curran, 2000). Others suggest that semantic priming (i.e., as indexed by the N400) simultaneously drives familiarity-based old/new judgments (Wilding & Ranganath, 2012; Yonelinas, 2002). Consistent with these proposals, in the present research, a more negative-going response was apparent on correct Stem 2 trials for both frontal (FN400) and centroparietal (N400) electrodes. Moreover, ERPs to correct (but not incorrect) Stem 2 facts were associated with performance on standardized measures of Concept Formation and Passage Comprehension. Whereas Concept Formation assesses the ability to identify novel relational understandings, Passage Comprehension taps the ability to comprehend meaning in context (i.e., according to cloze probability, or an eliciting word’s expectancy). Because the N400 is modulated as a function of cloze probability (Kutas & Hillyard, 1984), reflecting the ease with which current input is processed through comparison with prior, related knowledge (according to congruence), it is reasonable to conclude that differential processing between 400 and 600 msec indexes N400 activity and whether participants successfully identified the Stem 2 fact as novel yet related.

The present N400 findings also extend our current understanding of how comparison-based novelty detection triggers memory integration (Schlichting et al., 2014; Preston & Eichenbaum, 2013). Specifically, participants who exhibit a greater capacity to use prior semantic knowledge to generate predictions about upcoming information (i.e., they have high scores on the Passage Comprehension subtest) and to form novel conceptual understandings in the absence of prior knowledge (i.e., high scores on the Concept Formation subtest) exhibited less negative N400 amplitudes on trials on which they...
successfully integrated. This result may appear to contradict the trial-by-trial effect, in which more negative N400 responses were observed on correct versus incorrect trials. However, less negative N400 responses are similarly elicited when within-category violations are presented in high constraining versus low constraining sentences (e.g., “He caught the pass and scored another touchdown.” There was nothing he enjoyed more than a good game of baseball” vs. “After they unpacked the new refrigerator, they let Billy have his fun. He played for days afterwards with the big jar”). This effect has been attributed to the greater availability of memory-based predictions in high-constraining contexts (Federmeier & Kutas, 1999). That is, if the mismatch shares some overlap with the memory-based prediction (e.g., football and baseball are both sports), comparison of the available representations facilitates processing. With respect to the current research, if the preexisting memory trace is robust (Stem 1), participants will reactivate this knowledge upon experience of related information (Stem 2), which will guide detection of the deviation and facilitated processing of the relation. We may expect these processes to be more robust in individuals who scored high on the Passage Comprehension and Concept Formation subtests, respectively. This pattern is consistent with recent work demonstrating that encoding of overlapping events simultaneously elicits pattern separated (related events are coded by nonoverlapping neurons) and pattern integrated (related events are coded by overlapping neurons) representations, with integration signals predominating in cases in which prior knowledge is robust (Schlichting, Mumford, & Preston, 2015). Conversely, if the Stem 1 trace is weak or forgotten, Stem 2 will elicit either familiarity processing (i.e., this is old) or be treated as completely unrelated, respectively. In future research, it would thus be desirable to measure the strength of stem memory (an opportunity not available in the present research due to already high subject burden).

Three Additional Temporally Staged Processes Elicited after Initial Novelty Detection

Novelty detection has been proposed to initiate a host of additional encoding and retrieval processes aimed at resolving, integrating, and extending the semantic mismatch. Consistent with this notion, data-driven cluster-based permutation analyses revealed pronounced differences in processing of stem facts that were successfully versus unsuccessfully integrated; the differences were apparent in three additional latency windows. Because integration is first distinguished by what appears to be an N400, it is worth noting that, unlike other components, the latency of the N400 is highly consistent across many different paradigms. This suggests that the information extracted in this time window is constrained, thereby necessitating additional processing for other aspects of meaning. As such, additional effects related to semantic processing often follow the N400 as the semantic memory system “adds to, subtracts from, or otherwise modifies the activation that was established in the initial ‘sweep’” (Federmeier & Laszlo, 2009, p. 32).

One possible interpretation of the differential neural processing observed in the second encoding window for the Stem 1 (1183–1349 msec) and Stem 2 facts (1147–1297 msec) is that it reflects explicit comprehension of the semantic meaning conveyed. A common post-N400 ERP response that bares similarity to the effect observed consists of a frontal negativity, with greater amplitudes indexing processes associated with active meaning selection in response to perceived ambiguity (e.g., Lee & Federmeier, 2006). In the present research, ERP responses to stem facts that were unsuccessfully integrated elicited more negative responses, which was maximal at frontocentral and centroparietal sites. Thus, we may speculate that participants recruited greater neural resources in an attempt to interpret the ambiguous meaning of the presented information (e.g., cyanide is found in pips). If participants previously reactivated an intact representation of relevant information (e.g., apple seeds are called pips), explicit resolution of the new meaning conveyed should be facilitated. Conversely, if participants failed to reactivate related knowledge earlier or if the reactivated representation was insufficient, more effort would be required to access relevant content to comprehend the new meaning. Importantly, this frontal negativity was even more pronounced for the Stem 1 facts, of which participants had no prior knowledge from which to interpret the meaning. Stem 1 processing was also negatively associated with Digits Forward and Digits Backward in the prior encoding window (400–600 msec), suggesting that limited short-term and working memory spans might lead to initial difficulty forming sentence-level representations of the individually presented words. This further supports the interpretation that this later pronounced negativity indexes the difficulty of explicit comprehension more broadly, which is facilitated by prior reactivation/novelty in the case of correct Stem 2 trials.

Immediately following the post-N400 frontal negativity, a posterior positivity was observed between 1453 and 1647 msec. As discussed previously, post-N400 posterior positivity, referred to as the LPC or P600, has been linked to the process of representing relational knowledge in long-term memory (Bauer & Jackson, 2015). In the present research, greater posterior positivity was evident on Stem 2 trials in which participants failed to integrate, suggesting that more processing resources were needed to represent the updated relation between overlapping stem facts. Importantly, processing of Stem 1 facts did not differ as a function of performance. This finding suggests that participants might not have engaged in the same relational processing in the absence of knowledge to integrate and/or to resolve in memory (i.e., when presented with Stem 1 facts). It is worth noting that the typical LPC is observed around 500–900 msec poststimu-
lus onset. However, given that in the present research, the relation between to-be-integrated stem facts must be self-derived through reactivation and evaluation of prior knowledge, it is not surprising that this component would be elicited in a later time window. Support for this conclusion comes from the finding that this late posterior activity was also significantly correlated with explicit self-derivation at the explicit test for integration.

A similar pattern of posterior positivity observed during the 1453–1647 msec encoding window was again observed between 1173–1357 msec when participants were prompted to self-derive the novel integration fact. Again, larger amplitudes were elicited on unsuccessful trials, presumably reflective of the greater effort associated with extracting the target relation. In support of this interpretation, ERPs on successful trials were associated with measures of Concept Formation (e.g., novel relational reasoning) and moderately associated with Verbal Comprehension (e.g., the ability to reason based on previously learned information). Moreover, consistent with prior evidence showing that hippocampal activation during encoding of overlapping events is reinstated during a later inference test (Schlichting et al., 2014), we similarly demonstrated that Stem 2 posterior activity from 1453 to 1647 msec was positively correlated with the neural activity on successful self-derivation trials. Thus, the present results indicate that the neural activity associated with self-derivation is linked to relational reasoning based on prior knowledge. Yet further research is needed to determine whether the latest encoding window (1453–1647 msec) and self-derivation engaged common relational processes.

**Limitations**

The present results indicate that several temporally staged neurocognitive processes support the extension of semantic knowledge through memory integration. However, we acknowledge that interpretation of recorded ERP components is susceptible to the superposition problem. That is, multiple components are superimposed onto any one ERP waveform, making it difficult to decompose the mixture of underlying components. Thus, it is possible that the four ERPs elicted in the present research reflect a combination of additional processes (e.g., both reactivation and novelty detection between 400 and 600 msec). Further attempts must be made to fully disentangle these subprocesses through other experimental manipulations.

**Conclusion**

Using an ecologically valid test of self-derivation of new factual knowledge through integration of separate yet related episodes of new learning, the present research provides unique insight into time course of neurocognitive processing supporting this fundamental learning ability. Guided by the ERP and fMRI literatures, in addition to relations with standardized cognitive assessments, the present results implicate at least four temporally staged processes: (1) detection of a semantic deviation between novel and reactivated knowledge (400–600 msec), (2) comprehension and resolution of the semantic deviation (1122–1342 msec), (3) representation of the novel relation in long-term memory (1453–1647 msec), and (4) direct retrieval and/or recombination of previously integrated knowledge in response to a demand to self-derive new knowledge (1173–1357 msec during test). Whereas the results provided strong empirical support for the proposal that novelty detection triggers memory integration, because the ERPs elicited later in encoding were not associated with standardized measures, future research is needed to test the interpretations proffered. Similarly, despite some suggestion that common processes might be engaged during later encoding and test, without direct measures of memory for the individual stem facts it is difficult to determine whether failures at test were attributed to poor stem fact memory, poor integration, or both. Notwithstanding, this approach provides converging evidence for many of the processes previously implicated by fMRI research and informs how quickly these processes temporally unfold during integration of real-world factual knowledge.

**Acknowledgments**

This research was funded by NIH HD67359 to Patricia J. Bauer and by Emory College of Arts and Sciences and a James T. Laney Graduate School Dean’s Teaching Fellowship to Nicole L. Varga. The work was conducted in partial fulfillment of the requirements for the PhD at Emory University. The authors thank NLV’s dissertation committee—Jocelyn Bachevalier, Robyn Fivush, Joseph Manns, and Phillip Wolff—for helpful discussions and valuable feedback throughout this work. The authors especially extend their appreciation to Joseph Manns for substantive input on and assistance with the data analytic plan. The authors also thank Amanda Broyles and Manas Winfield for assistance with stimulus development and data collection, as well as other members of the Memory at Emory laboratory group for their help with various aspects of the research. The authors additionally extend their gratitude to the individuals who participated in the research, without whom this work would not have been possible.

Reprint requests should be sent to Nicole L. Varga, Department of Psychology, Emory University, 56 Eagle Row, Atlanta, GA 30322, or via e-mail: nvarga@emory.edu.

**REFERENCES**


Journal of Cognitive Neuroscience