

# Intracranial EEG Correlates of Expectancy and Memory Formation in the Human Hippocampus and Nucleus Accumbens

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## SUMMARY

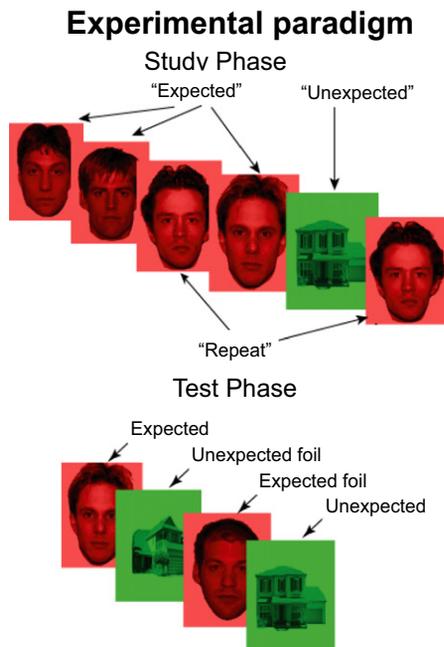
The human brain is adept at anticipating upcoming events, but in a rapidly changing world, it is essential to detect and encode events that violate these expectancies. Unexpected events are more likely to be remembered than predictable events, but the underlying neural mechanisms for these effects remain unclear. We report intracranial EEG recordings from the hippocampus of epilepsy patients, and from the nucleus accumbens of depression patients. We found that unexpected stimuli enhance an early (187 ms) and a late (482 ms) hippocampal potential, and that the late potential is associated with successful memory encoding for these stimuli. Recordings from the nucleus accumbens revealed a late potential (peak at 475 ms), which increases in magnitude during unexpected items, but no subsequent memory effect and no early component. These results are consistent with the hypothesis that activity in a loop involving the hippocampus and the nucleus accumbens promotes encoding of unexpected events.

## INTRODUCTION

A critical function of the human brain is to extract patterns from recent events in order to generate predictions about the future (Grossberg, 1976; 2003; Friston, 2005; Schacter et al., 2007). Violations of such predictions activate a distributed network involved in orienting to and encoding novel events, thereby re-

sulting in enhanced memory formation (Rescorla and Wagner, 1972; Tulving et al., 1996; Ranganath and Rainer, 2003). According to one model based on animal studies, the hippocampus may initially compute a novelty signal (as the difference between a predicted stimulus and an actual stimulus), which is propagated to the nucleus accumbens (Lisman and Grace, 2005). The nucleus accumbens—in close interaction with the dopaminergic midbrain (e.g., Montague et al., 1996; Schultz et al., 1997; Zaghoul et al., 2009)—is thought to relay information about expectancy, salience, and goal information, thereby influencing dopaminergic modulation of hippocampal long-term potentiation and encoding of unexpected stimuli or events (Marciani et al., 1984; Li et al., 2003; Lemon and Manahan-Vaughan, 2006). This model predicts two neural signatures of expectancy in the hippocampus, an earlier and a later one; the later one should be associated with enhanced memory for unexpected items. Furthermore, it predicts that an expectancy signal is computed in the hippocampus first and then transferred to the nucleus accumbens. These predictions on the temporal order in which novelty and memory are computed in different brain structures remain to be tested, however.

Here, we report results of intracranial electroencephalography (EEG) studies aimed at clarifying the relationship between novelty processing and memory formation in the hippocampus and nucleus accumbens. Two groups of patients participated in this study: one group of eight patients with medication-resistant epilepsy had electrodes implanted in the hippocampus in order to localize the seizure foci. Another group of six patients had electrodes implanted in the nucleus accumbens for an experimental trial of deep brain stimulation for medically intractable depression (Schlaepfer et al., 2008; Bewernick et al., 2010). More details about the participants are provided in the [Supplemental Information](#), available online.



**Figure 1. Overview of the Paradigm**

The paradigm included a Study Phase (encoding of items, top) and a Test Phase (retrieval, bottom). In both phases, a majority of items belonged to one category with respect to background color and content (expected items; e.g., red faces), while a minority of items were deviant (unexpected items; e.g., green houses). See also Table S1 for behavioral data.

We examined the effect of unpredicted events on memory by using a version of the “Von Restorff” paradigm (Von Restorff, 1933) in which participants studied pictures of faces and houses shown in grayscale against a red or green background (Figure 1). While the majority of items came from one category (“expected items;” e.g., faces on a red background), a small proportion of interleaved stimuli came from the other category (“unexpected items;” e.g., houses on a green background) in a balanced design (see Supplemental Information). Participants were subsequently tested on memory for the expected and unexpected items from each list, allowing us to examine encoding activity as a function of subsequent memory performance.

## RESULTS

Corrected recognition scores (confident hits minus false alarms) in epilepsy patients were significantly better for unexpected than for expected items ( $29.9 \pm 6.7$  versus  $20.5\% \pm 4.3\%$ ;  $t_7 = 2.49$ ;  $p < 0.05$ ). This difference was in the same direction in the group of depression patients, although it was not statistically significant ( $25.9\% \pm 5.4\%$  versus  $22.2\% \pm 4.6\%$ ;  $t_5 = 0.54$ ;  $p = 0.66$ ). The nonsignificant Von Restorff effect in depression patients is probably due to the relatively low sample size (see Supplemental Information for further information). Moreover, a two-way ANOVA revealed that performance in the two groups was not significantly different ( $F_{1,12} = 0.03$ ;  $p = 0.87$ ), and that there was no interaction between group and unexpected versus

expected items ( $F_{1,12} = 0.475$ ;  $p = 0.5$ ) (for details, see Table S1, available online). In both groups, reaction times during encoding (i.e., related to the pleasant/unpleasant rating of items) were significantly slower for unexpected than expected items (epilepsy patients:  $t_7 = 3.88$ ;  $p < 0.01$ ; depression patients:  $t_5 = 2.98$ ;  $p < 0.05$ ), suggesting that expectancy was processed similarly.

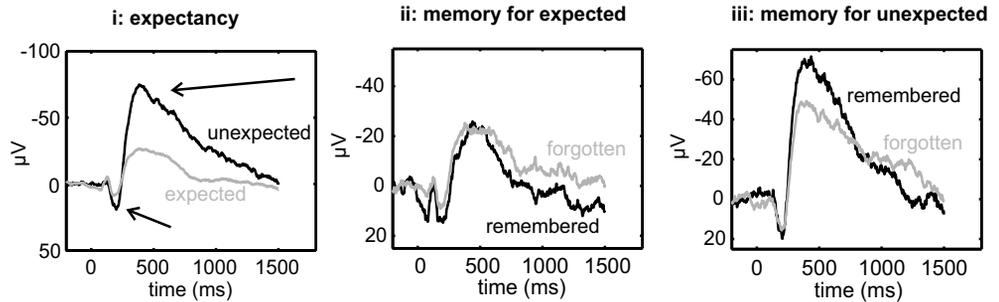
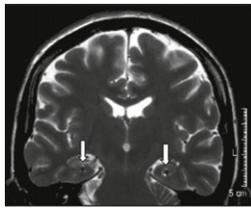
Event-related potentials (ERPs) recorded from the hippocampus revealed an early positive peak at  $186.9 \pm 16.7$  ms (mean  $\pm$  SEM) and a later negative peak at  $481.5 \pm 63.3$  ms, which resembled the hippocampal P300 potential (Halgren et al., 1980; Smith et al., 1990; Knight, 1996; Soltani and Knight, 2000; Polich, 2007). Both components were significantly larger during processing of unexpected as compared with expected stimuli (early component:  $t_7 = 2.64$ ;  $p < 0.05$ ; late component:  $t_7 = 3.91$ ;  $p < 0.01$ ; Figure 2A). Effects of repeat items are shown in Figure S1. Moreover, a two-way ANOVA for the late component with “expectancy” and “memory” as repeated-measures revealed a significant main effect of expectancy ( $F_{1,7} = 9.64$ ;  $p < 0.05$ ) and a highly significant expectancy  $\times$  memory interaction ( $F_{1,7} = 12.92$ ;  $p < 0.01$ ), but no main effect of memory ( $F_{1,7} = 3.31$ ;  $p > 0.1$ ). Subsequent two-tailed *t* tests revealed an increased late potential during encoding of subsequently remembered as compared with forgotten unexpected items ( $t_7 = 2.72$ ;  $p < 0.05$ ), but no subsequent memory effect for expected items ( $t_7 = 0.07$ ;  $p > 0.9$ ). A similar analysis on the early component revealed no significant effect of memory ( $F_{1,7} = 3.45$ ,  $p > 0.1$ ) and no expectancy  $\times$  memory interaction ( $F_{1,7} = 1.07$ ,  $p > 0.1$ ).

As noted above, some models suggest that the late-onset expectancy effects in the hippocampus might be modulated by a saliency signal conveyed by the nucleus accumbens (Lisman and Grace, 2005). We therefore investigated electrophysiological correlates of expectancy processing in the patients with electrodes in this region. Visual inspection of the EEG traces recorded within the nucleus accumbens revealed a negative deflection with a latency of  $475.2 \pm 177.2$  ms (mean  $\pm$  SEM; Figure 2B). This ERP component was significantly larger for unexpected compared with expected items ( $t_5 = 3.82$ ;  $p < 0.05$ ). A two-way ANOVA on this component revealed no main effect of memory ( $F_{1,5} = 0.171$ ;  $p > 0.6$ ) and no interaction ( $F_{1,5} = 0.274$ ;  $p > 0.6$ ). Furthermore, no early potential as in the hippocampus became apparent, and statistical comparison of expected and unexpected trials in the same window as in the hippocampus did not reveal a difference ( $t_5 = 0.52$ ;  $p > 0.5$ ).

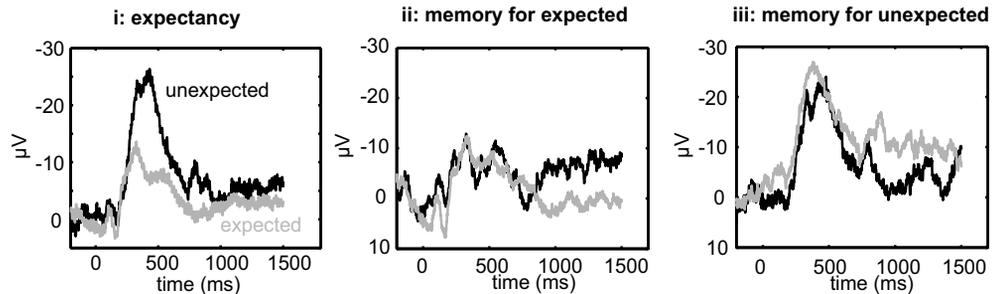
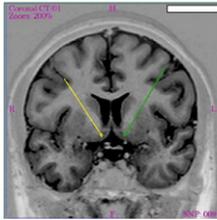
To further explore the neural signature underlying processing of unexpected items, we conducted time-frequency analyses of activity within the hippocampus and nucleus accumbens. As shown in Figure 3A, the most pronounced difference between processing of unexpected and expected items in the hippocampus was an early (200–400 ms) increase and later (500–1400 ms) decrease of theta band activity, and an increase between 500–700 ms and 1000–1100 ms in the high gamma (70–90 Hz) frequency range (statistical analyses are described in the Supplemental Results).

The data presented thus far only provide indirect evidence for hippocampal-accumbens information transfer, because the nucleus accumbens and hippocampal ERPs were recorded in separate patient groups. However, two additional analyses

**A Hippocampus ERPs**



**B Ncl. accumbens ERPs**



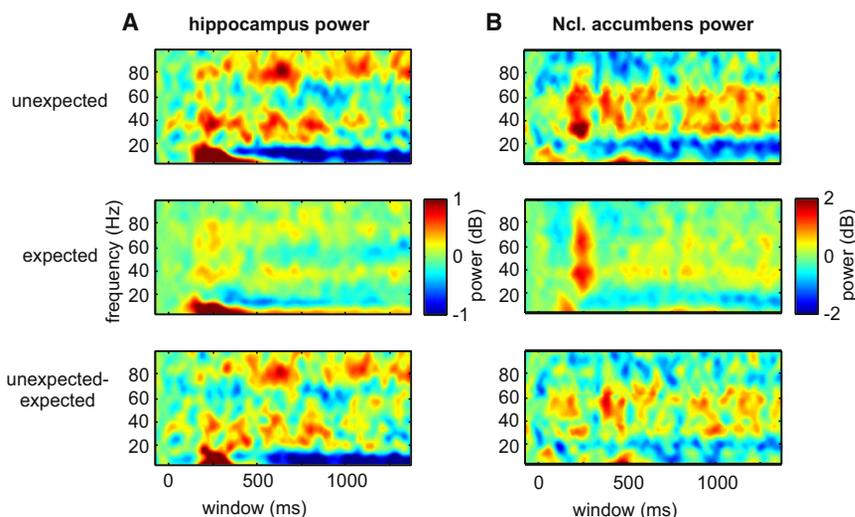
**Figure 2. Event-Related Potentials in Hippocampus and Nucleus Accumbens**

(A) ERPs from the hippocampus. (Left) Postimplantation MRI of an epilepsy patient implanted with bilateral depth electrodes in the hippocampus. (Ai–Aiii) Hippocampal ERPs during processing of items of different types in the Study Phase. (Ai) Enhancement of hippocampal early and late ERP components during processing of unexpected as compared with expected items. (Aii and Aiii) The late ERP component in the hippocampus reflects the interaction of expectancy and subsequent memory.

(B) (Left) Image acquired during MRI-guided stereotactic implantation of bilateral electrodes for deep brain stimulation in the nucleus accumbens of depression patients. (Bi) Expectancy effect on the nucleus accumbens ERPs. (Bii and Biii) No effect of subsequent memory as in the hippocampus became apparent. See also Figure S1 for effects of repeat items.

were conducted to assess functional connectivity in our data. First, we used data from two epilepsy patients who were implanted not only with hippocampal depth electrodes, but also with extensive subdural strip and grid electrodes (>100 electrode contacts; see Figure S2), to conduct a source analysis of activity within the nucleus accumbens (Dümpelmann et al., 2009; see Supplemental Experimental Procedures). In this analysis, nucleus accumbens activity was estimated using activity from

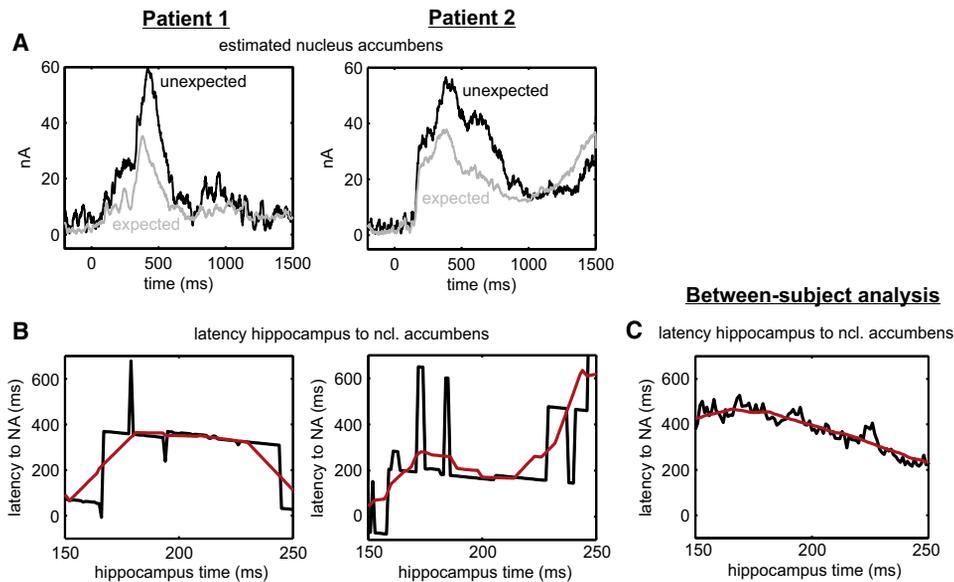
subdural grid and strip electrodes (not from hippocampal depth electrodes) as input. In both patients, the reconstructed time courses of activity within the nucleus accumbens were qualitatively very similar to the time courses of nucleus accumbens activity measured in the depression patients (Figure 4A). Unexpected items elicited larger components in the same time window as for the measured data. In these two patients, we calculated functional connectivity between the (measured)



**Figure 3. Time-Frequency Analyses of Recordings from the Hippocampus and Nucleus Accumbens**

(A) Theta (3–8 Hz) power is first (200–400 ms) increased and later (500–1400 ms) decreased during processing of unexpected as compared with expected items in the hippocampus. Higher (70–90 Hz) gamma power is selectively increased in the hippocampus during processing of unexpected items between 500–700 and 1000–1100 ms. The color bar applies to all power plots.

(B) No significant differences were observed in the nucleus accumbens.



**Figure 4. Cross-Correlation of Activity in Hippocampus and Nucleus Accumbens**

(A) Estimated time courses of activity in the nucleus accumbens based on source reconstruction of intracranial EEG data.

(B) Latency of (estimated) nucleus accumbens activity with maximal cross-correlation to (recorded) hippocampal activity around the peak of the early novelty response in the hippocampus.

(C) Between-subject analysis of cross-correlation (hippocampal patients versus nucleus accumbens patients). Black lines indicate raw values; red lines, moving averages (time window of 30 ms).

See also Figure S2 for implantation schemes of the two patients with reconstructed nucleus accumbens activity.

hippocampal activity and the (reconstructed) nucleus accumbens activity. The hypothesis that unexpected information is detected in the hippocampus and transferred to the nucleus accumbens predicts that activity around the early hippocampal component (peaking at 187 ms) is correlated with the later component in the nucleus accumbens (with a peak at 475 ms). Thus, hippocampal activity at around 150–250 ms should correlate with activity around 300 ms later in the nucleus accumbens. We thus calculated cross-correlations across trials (i.e., single-trial amplitude covariance; e.g., Truccolo et al., 2002) for hippocampal activity around the early component (between 150 and 250 ms) with all time points in the nucleus accumbens. Next, for each of these hippocampal time points, we searched for the nucleus accumbens time point with the maximal correlation value. Figure 4B depicts the latency between hippocampal and nucleus accumbens time points with maximal correlation. In both patients, we found that hippocampal activity in this time window correlated highest with nucleus accumbens activity 200–400 ms later, consistent with the predicted lag of 300 ms. Notably, latencies were relatively constant across several tens of milliseconds in this time interval (see the plateaus of latency values), indicating that contiguous amplitude values in the hippocampus are maximally correlated with contiguous amplitude values in the nucleus accumbens. To assess the significance of this correlation, we calculated average correlation values during this plateau—i.e., averaged across all points in time between 150 and 250 ms when latencies were between 200 and 400 ms. Indeed, we found a significant correlation in this range in both patients (patient 1:  $R = 0.183$ ;  $t_{268} = 3.05$ ;  $p < 0.005$ ; patient 2:  $R = 0.1251$ ;  $t_{279} = 2.106$ ;  $p < 0.05$ ).

Second, we calculated single-trial amplitude covariance between activity in epilepsy and depression patients. Our reasoning for this relatively unusual measure of between-subject amplitude correlation was that the specific temporal pattern of expected and unexpected items would induce systematic fluctuations of EEG amplitudes—e.g., related to primacy, recency, and temporal variations of expectations (Hasson et al., 2004; Lindenberger et al., 2009). These fluctuations should be visible both in the hippocampus and in the nucleus accumbens, because in each patient, identical sequences of items were presented in corresponding blocks. We thus calculated correlations across trials for all pairs of hippocampal and nucleus accumbens patients. Only corresponding trials which were free of artifacts in both patients of each pair were analyzed. Again, we predicted that hippocampal activity between 150 and 250 ms should be maximally correlated with nucleus accumbens activity around 300 ms later. Figure 4C shows that we observed a peak correlation at a latency of around 300–400 ms. In all but one pair, correlation values (calculated as for the within-subject analysis) were significant (mean  $R = 0.206$ ; range: 0.169–0.303; range of  $p$  values: 0.0001–0.047).

## DISCUSSION

Our findings show that it is possible to estimate the relative sequence of processes in the human hippocampus and nucleus accumbens: whereas the early hippocampal and the (later) nucleus accumbens components were modulated only by expectancy, the late hippocampal component was correlated with both expectancy and subsequent memory, and likely

reflects the interaction of these processes. Thus, our data are in close agreement with the model by [Lisman and Grace \(2005\)](#). They are consistent with the idea that hippocampal activity may initially signal the occurrence of an unexpected event, and that the nucleus accumbens may influence subsequent hippocampal processing, which serves to promote memory encoding.

Previous studies using intracranial EEG recordings in epilepsy patients reported neural correlates both of unexpected items ([Halgren et al., 1980](#); [Grunwald et al., 1999](#); [Vanni-Mercier et al., 2009](#)) and of memory formation ([Fernández et al., 1999](#)), but not on the interaction of these stimulus properties. Unexpected or contextually deviant items are known to induce an increased novelty P300 response in scalp EEG recordings. Lesion studies and intracranial EEG recordings demonstrated that this potential depends on a network including the hippocampus ([Halgren et al., 1980](#); [Knight, 1996](#)), as well as the frontal lobe ([Knight, 1984](#); [Baudena et al., 1995](#)) and the temporoparietal junction ([Knight et al., 1989](#); [Halgren et al., 1995](#)) (for reviews, see [Soltani and Knight, 2000](#); [Polich, 2007](#)). Recently, single-neuron studies in monkeys showed that neurons in the basal forebrain increase their firing rates upon presentation of unexpected reinforcements ([Lin and Nicolelis, 2008](#)), and transfer this motivational signal to the prefrontal cortex ([Lin et al., 2006](#)). EEG studies on the mismatch negativity (MMN), in which a deviant auditory or visual stimulus is presented among a majority of standard stimuli, found that this potential is generated in primary sensory cortices (e.g. [Näätänen et al., 1978](#); [Cammann, 1990](#)), but appears to be facilitated by processes within the prefrontal cortex, because it is reduced in patients with lesions in this region ([Alain et al., 1998](#)). In this study, MMN was unaffected in patients with hippocampal lesions. These findings suggest that the occurrence of an unexpected event likely recruits a network of brain regions that extends well beyond the hippocampus and nucleus accumbens, and these other regions might play a prominent part in the detection of contextual deviance.

In a previous study using a word-list learning paradigm, [Fernández et al. \(1999\)](#) found subsequent memory effects on late positive potentials in the hippocampus. These effects were not observed in the current study, possibly due to differences in task characteristics and material: first, no manipulation of expectancy was conducted in the Fernández study; second, words instead of pictorial stimuli were used; finally, free recall was tested in the study by Fernández and colleagues, which depends on conscious access to a memory trace, whereas we measured recognition memory. The latter difference might be particularly important because recognition memory in our study may rely on both stimulus familiarity and conscious recollection ([Yonelinas, 2001](#)).

Our recordings from the nucleus accumbens are among the first intracranial EEG data recorded from humans in this region. By recording data from six patients with therapy-refractory major depression undergoing deep brain stimulation ([Schlaepfer et al., 2008](#); [Bewernick et al., 2010](#)), we observed negative ERPs peaking at around the same time as the hippocampal late component, which were significantly larger during processing of unexpected as compared with expected items. The fact that we observed an early potential sensitive to expectancy in the hippocampus, but not in the nucleus accumbens, suggests that the nucleus ac-

cumbens receives expectancy information from the hippocampus, and then back-projects to the hippocampus to facilitate memory for unexpected items. The nucleus accumbens consists mainly of inhibitory GABAergic medium spiny neurons and does not appear to project directly to the hippocampus (e.g., [Thierry et al., 2000](#)). However, it is a major relay station between the hippocampus and the dopaminergic ventral tegmental area (VTA; [Floresco et al., 2001](#); [2003](#)). Indeed, novelty exploration leads to release of dopamine within the nucleus accumbens via the subiculum and the VTA ([Legault and Wise, 2001](#)) and within the hippocampus ([Li et al., 2003](#)). Dopamine facilitates long-term potentiation within the hippocampus via activation of dopaminergic D1/D5 receptors ([Marciani et al., 1984](#); [Li et al., 2003](#); [Lemon and Manahan-Vaughan, 2006](#)). We thus suggest that the backward projection from the nucleus accumbens to the hippocampus is accomplished via dopaminergic neurons within the VTA.

Supplementary time-frequency analyses demonstrated a role for hippocampal theta and high gamma oscillations in processing of unexpected information. The initial increase and subsequent decrease in hippocampal theta for unexpected events are possibly related to the late hippocampal component, which has a frequency composition in the delta/theta band. Indeed, a previous intracranial EEG study using an oddball paradigm showed that the hippocampal P300 component was associated with an early (200–500 ms) increase and a later (500–1000 ms) decrease in theta power ([Fell et al., 2004](#)), very similar to the results from our current study. Hippocampal theta activity in rats depends on at least two different generators (reviewed in [Buzsáki, 2002](#)). Inputs from the entorhinal cortex induce theta oscillations that persist after antagonism to muscarinic acetylcholine. In contrast, projections from the medial band of broca and septum cause a tonic cholinergic excitation and phasic GABAergic inhibition of hippocampal basket cells, which induce rhythmic inhibitory postsynaptic potentials in the theta frequency range on their target pyramidal cells in the CA1 region.

Animal experiments showed that dopaminergic inputs to the hippocampus indeed affect hippocampal theta oscillations (and may subsequently also alter theta-related ERPs). The septum receives projections from the dopaminergic midbrain, which increase the firing rate of septal neurons and may thus enhance hippocampal theta band activity ([Fitch et al., 2006](#)). Hippocampal theta band activity is also directly affected when dopamine is released into the hippocampus: activation of dopamine receptors increases the extracellular concentration of acetylcholine ([Acquas et al., 1994](#)), which in turn activates muscarinic acetylcholine receptors and thus enhances hippocampal theta power ([Brazhnik et al., 1993](#); [Chapman and Lacaille, 1999](#); [Fellous and Sejnowski, 2000](#)). Lesions to the septum ([Yoder and Pang, 2005](#)) or the VTA ([Orzei-Gryglewska et al., 2006](#)) significantly reduce hippocampal theta power. Taken together, these results suggest that hippocampal theta oscillations—and thus also the late hippocampal component—may be affected via multiple pathways by dopaminergic neurons in the VTA: either directly due to intrahippocampal release of dopamine, or indirectly by release of dopamine into the septum, which enhances hippocampal theta by cholinergic and GABAergic projections.

One limitation of our study is that nucleus accumbens and hippocampal activity were recorded in two different groups of subjects, and therefore the data only provide an indirect measure of functional connectivity between these brain regions. This is a necessity, however, because the location of electrode placements in human patients must be dictated solely by clinical considerations, and to our knowledge, there are no conditions that would require electrode placement in both hippocampus and nucleus accumbens. To indirectly address the idea that novelty information is transferred from the hippocampus to the nucleus accumbens, we calculated cross-correlations between hippocampal amplitudes around the time of the early potential with estimated nucleus accumbens time courses (in the same patients) and measured activity in the depression patients. Results from both analyses are consistent with the proposed information transfer from the hippocampus to the nucleus accumbens, but correlations between the nucleus accumbens component and the late hippocampal potential were less clear (see [Supplemental Information](#)). However, it should be noted that both measures have their limitations. Time courses in the nucleus accumbens were estimated using anatomically defined regions of interest in patients with extensive implantation schemes. Although source analyses based on intracranial EEG data are most likely more accurate than source reconstruction based on surface EEG because they avoid the spatial low-pass filter properties of the skin and bone (e.g., [Fuchs et al., 2007](#)), reconstruction of activity from deep brain structures is notoriously difficult. The estimated time courses in the nucleus accumbens resembled those that were recorded in depression patients; however, a validation of this analysis in animals with both subdural and nucleus accumbens electrodes would be useful. Our second analysis—correlation of amplitudes between subjects relying on joint intertrial variability across the experiment—is complicated by the variability of single-trial responses between subjects. Again, it would be necessary to test this approach in animals with electrodes in both regions.

All recordings in this study were obtained in patients. Thus, we cannot exclude that our findings are influenced by disease-related factors. In particular, it is very likely that depression results in dysfunction of dopaminergic transmission ([Randrup et al., 1975](#); [Dunlop and Nemeroff, 2007](#)), which could have influenced the behavioral or EEG results. However, several considerations cast doubt on the idea that pathology contributed significantly to our results: first, there was no evidence for a qualitative difference in memory performance between the two patient groups. Second, there was no evidence for a correlation between depression values and Von Restorff effects. Third, reaction times during encoding of unexpected and expected items differed in both groups, further suggesting that expectancy effects were behaviorally similar regardless of subjects' pathology. Fourth, other findings from this patient group are consistent with data from animal recordings and with existing theories on reward processing and action monitoring within the nucleus accumbens ([Münte et al., 2007](#); [Cohen et al., 2009a, 2009b](#)): the amplitude of nucleus accumbens ERPs scales with the size of anticipated and received rewards ([Cohen et al., 2009a](#)), as described earlier in fMRI studies (e.g., [Knutson et al., 2001](#)), and is associated with incorrect responses during

a Flanker task ([Münte et al., 2007](#)), in line with a role of this structure in action monitoring ([Goto and Grace, 2005](#)). Finally, nucleus accumbens time-frequency responses predict strategy changes during reversal learning ([Cohen et al., 2009b](#)), consistent with previous findings that gating of oscillatory activity within the nucleus accumbens is relevant for reinforcement learning (e.g., [Goto and Grace, 2005](#); [Block et al., 2007](#)). Concerning the epilepsy patients, intracranial EEG data from these patients were recorded from regions outside of the seizure onset zone (see [Experimental Procedures](#)). It has previously been shown at least for oddball paradigms that ERPs that are acquired in the hemisphere contralateral to the seizure origin are qualitatively similar to potentials in healthy monkeys during the same task ([Paller et al., 1992](#)).

In general, intracranial EEG data may serve to bridge the gap between functional neuroimaging studies in human subjects and electrophysiological recordings in animals. More specifically, our data show that detection of unexpected items is associated with two separable processes in the hippocampus, and that only the latter one is also related to memory encoding. Such a distinction between two events with an interval of only a few hundreds of milliseconds cannot be made using fMRI. Furthermore, our results show that the nucleus accumbens is also activated by unexpected items, which was found in some ([Zink et al., 2003, 2006](#)), but not all ([Bunzeck and Düzal, 2006](#)), previous fMRI studies with related paradigms. Apart from differences in the experimental design, this divergence might be related to the fact that ERPs may be more sensitive to changes in neural activity than the BOLD response is ([Axmacher et al., 2009](#)). Functionally, our findings indicate that the same regions that are crucial for processing of rewarding items are also activated by unexpected items, consistent with the idea that novel items are salient per se ([Zink et al., 2003, 2006](#); [Bunzeck and Düzal, 2006](#); [Wittmann et al., 2008](#)). Finally, the relative timing of expectancy effects in the hippocampus and nucleus accumbens suggests that these structures interact not only during reward processing, as shown previously in animal experiments (e.g., [Tabuchi et al., 2000](#); [Lansink et al., 2009](#)), but also during processing of unexpected information in general.

In summary, whereas the early hippocampal and the later nucleus accumbens components were modulated only by expectancy, the late hippocampal component was modulated by both expectancy and subsequent memory. We suggest that this later process reflects the interaction of novelty signaling and memory encoding. Taken together, these results speak to the relative timing of expectation effects in different regions of the human brain, and they support models of accumbens-hippocampus interactions during encoding of unexpected events.

## EXPERIMENTAL PROCEDURES

### Epilepsy Patients with Hippocampal Electrodes

Eight patients with pharmacoresistant temporal lobe epilepsy (six female; mean age  $\pm$  SD: 31.3  $\pm$  8.2 years) participated in the study. Recordings from these patients were performed at the Department of Epileptology, University of Bonn, Germany. The study was approved by the local ethics committee, and all patients gave written informed consent. MRI scans revealed unilateral Ammons Horn sclerosis in five patients, one presented with loss of gray-white matter differentiation in the left temporal pole, and two showed no visible

pathology. No seizure occurred in any of the patients during the 24 hr preceding the experiment. All patients had bilateral hippocampal depth electrodes that were implanted for diagnostic purposes using a computerized tomography-based stereotactic insertion technique (Van Roost et al., 1998). We included only patients with a depth electrode in a morphologically intact hippocampus (as defined by MRI). In all eight patients, a seizure onset zone outside of the hippocampus from which data are presented was identified during clinical monitoring. All eight patients subsequently underwent surgery. There was an improvement in seizure frequency and severity in all patients, and six of them became completely seizure free. The location of electrode contacts was ascertained by MRI in each patient (see Figure 2A for a typical example of an electrode in the hippocampus). Electrodes (AD-Tech, Racine, WI, USA) had 10 cylindrical platinum-iridium contacts and a diameter of 1.3 mm. Recordings were performed using a Stellate recording system (Stellate GmbH, Munich, Germany). On average, each patient had  $5.8 \pm 1.2$  (mean  $\pm$  SD) hippocampal contacts.

#### Depression Patients with Nucleus Accumbens Electrodes

Six patients (three female; mean age  $\pm$  SD:  $49.2 \pm 10.8$  years) suffering from treatment-refractory major depressive disorder participated in this study. These patients were included in an experimental clinical trial of deep brain stimulation for treatment of pharmacoresistant depression. All patients suffered from extremely refractory forms of depression and did not respond to pharmacotherapy, psychotherapy, and electroconvulsive therapy. A detailed description of the inclusion criteria can be found elsewhere (Schlaepfer et al., 2008). Electrodes were implanted bilaterally in the nucleus accumbens. Electrode placement was planned using MRIs and computer-assisted technology, as described previously (Sturm et al., 2003). Each electrode had four contacts in total that were located in the following regions: shell of the nucleus accumbens (most distal contact), core of the nucleus accumbens (one contact), and internal capsule (two contacts). Figure 2B shows the exact placement of the electrodes in one patient. Electrodes (Medtronic, MN, USA) had four cylindrical platinum-iridium contacts and a diameter of 1.3 mm. Recordings were performed using a Stellate recording system (Stellate GmbH, Munich, Germany). After the recording session, electrodes were used for permanent electrical stimulation of the nucleus accumbens (clinical results are reported in Schlaepfer et al., 2008, and Bewernick et al., 2010). The location of electrode placement was made entirely on clinical grounds and was verified by intraoperative X-ray. This experiment, and the larger clinical study of the use of deep brain stimulation as a treatment option for major depression, was approved by the ethics committees at the Universities of Bonn and Cologne. The clinical study is registered with the Trials Registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) under the number NCT00122031.

#### Experimental Design

For each patient, the experiment was conducted across a series of sessions, each of which lasted approximately 15 min, and included a familiarization phase, an encoding phase, and a retrieval phase. During the familiarization phase, the four stimuli to be used on “repeat” trials (see below) were each presented four times in a random sequence. EEG data reported here were recorded during the encoding phases, during which 112 pictures were presented. As shown in Figure 1A, the majority of study stimuli, termed expected items, in each block of study trials (72%) were trial-unique stimuli from one category (either faces or houses). On a small percentage of trials (14%), termed unexpected items, stimuli were trial-unique items from the minority category. Based on previous studies of the Von Restorff effect, it was hypothesized that memory performance would be enhanced for unexpected, as compared with expected, items. Finally, on a small percentage of trials (14%), termed repeats, stimuli were from the same category as those presented on expected trials, but participants were prefamiliarized to the repeat stimuli, and these stimuli were also repeatedly presented throughout the experiment. These stimuli were included to assess neural responses to relatively infrequent events (Sutton et al., 1965), even when no episodic encoding would be required (because the stimuli were well-learned even before the beginning of the experiment). Our design does not allow the distinction between effects of background color and picture category. We aimed at introducing a maximal effect of expectancy and thus varied these properties in

parallel; further studies are necessary to distinguish whether different types of novelty signals are processed in the same way.

On each encoding trial, a house or face was presented, for 2500 ms, and subjects were asked to rate each as pleasant or unpleasant by pressing one of two mouse buttons. This task was administered to ensure that participants adequately attended to and processed each item. All responses were performed by making a right-handed button press. The intertrial interval was 1500 ms. The order of all trials was pseudorandomized using an m-sequence (Buracas and Boynton, 2002), with the condition that unexpected trials could never occur consecutively.

In the subsequent retrieval phase, subjects were presented with 72 test items: 32 of these items were previously shown on expected trials during the study phase, 16 were new items from the same category as expected items, 16 were old items that were previously shown on unexpected trials during the study phase, and 8 were new items that were from the same category as unexpected items. On each trial, subjects were asked to make a button press to indicate their confidence on a four-point scale as to whether the picture had been shown during the previous study phase. Each test stimulus was presented for 5000 ms with a 1500 ms intertrial interval. Each patient completed up to eight recording sessions. Of the eight patients with medial temporal lobe depth electrodes, six completed all eight sessions, one patient completed six sessions, and one completed four sessions. Different sets of stimuli were used for each session with the exception of the stimuli used on repeat trials, which were the same in each session.

#### Recording and Analyses

Depth EEG recordings were referenced to linked mastoids, recorded at a sampling rate of 1000 Hz, and band-pass filtered (0.01 Hz [6 dB/octave] to 300 Hz [12 dB/octave]). EEG trials were visually inspected for artifacts (e.g., epileptiform spikes), and trials with artifacts were excluded from further analysis. Group statistical analyses were performed by analyzing data from one contact in the hippocampus in each patient. All recordings were taken from the nonfocal hemisphere (i.e., contralateral to the epileptogenic focus), to minimize the possibility of artifact contamination. Previous studies that bear functional similarities to the experiments presented here reported P300-like potentials in the hippocampus following presentation of rare or unexpected items (Halgren et al., 1980; Knight, 1996; Polich, 2007). Accordingly, recordings were analyzed from the contact with the maximal P300-like potential (i.e., the electrode with the maximal negative peak potential in a window between 100 and 700 ms). Importantly, the site was determined after averaging across trial types (expected, unexpected, and repeat trials) to avoid any bias in the selection of the electrodes. Furthermore, the observed effects (see main manuscript) were unrelated to the electrode selection criterion, because we observed qualitatively identical results if responses from all electrodes within the hippocampus (and nucleus accumbens, respectively) were averaged (see Supplemental Results). After electrode selection, we analyzed ERPs in the following time windows: the early component in the hippocampus was analyzed as the maximum value in a time window between 100 and 300 ms (in each patient, there was a visible peak in this interval). The late component was analyzed in the same interval between 100 and 700 ms in the hippocampus and the rhinal cortex. Data were analyzed using the EEGLAB package (Delorme and Makeig, 2004) running with MATLAB (The Mathworks, Natick, MA, USA) as well as with our own MATLAB programs. *p* values in the ANOVAs were corrected for violations of sphericity using the Huynh-Feldt procedure (Huynh and Feldt, 1976). In analyses of recordings from the nucleus accumbens, we also chose the electrode with the most negative peak ERP in a window between 100 and 700 ms (averaged across all conditions) and analyzed the amplitude as the maximum potential in this window.

#### SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes two figures, one table, Supplemental Data, and Supplemental Experimental Procedures and can be found with this article online at [doi:10.1016/j.neuron.2010.02.006](https://doi.org/10.1016/j.neuron.2010.02.006).

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