

RAPID COMMUNICATION

An Epigenetic Induction of a Right-Shift in Hippocampal Asymmetry: Selectivity for Short- and Long-Term Potentiation but Not Post-Tetanic Potentiation

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ABSTRACT: In humans, it is well established that major psychological functions are asymmetrically represented between the left and right cerebral cortices. The developmental origin of such functional lateralization remains unknown. Using the rat as a model system, we examined whether exposing neonates briefly to a novel environment can differentially affect synaptic plasticity in the left and right hippocampi during adulthood. During the first 3 weeks of life, one half of the pups from a litter spent 3 min daily away from their familiar home environment (Novel) while their littermates remained in that familiar environment (Home). At adulthood (7-months old), post-tetanic potentiation (PTP) of excitatory post-synaptic potentials (EPSPs), a very short-lasting form of plasticity, was greater among the Novel than the Home rats in both left and right hippocampi. In contrast, the novelty-induced increases in short- and long-term potentiation (STP, LTP), two relatively longer-lasting forms of plasticity, were found only in the right hippocampus. These findings demonstrate that a phase-selective asymmetry in hippocampal synaptic plasticity can be induced epigenetically by seemingly small systematic differences in early life environment. The selectivity of this asymmetry for the longer-lasting forms of synaptic plasticity suggests that the observed asymmetry in plasticity may contribute specifically to an asymmetric learning process which, in turn, may contribute to a functional asymmetry in the neocortex. © 2007 Wiley-Liss, Inc.

KEY WORDS: novelty; lateralization; memory; early experience; synaptic plasticity

INTRODUCTION

Brain asymmetry is an evolutionarily ancient neural organizational phenomenon present in both mammalian and nonmammalian brains (Vallortigara and Rogers, 2005). In humans, it appears to be omnipresent in major psychological functions, including perception, action, memory, emotion, and language (for review see Davidson and Hugdahl, 1995; Gazzaniga, 2000), and can serve as a marker for various forms of psychopathology (Davidson, 2003). While major theories have focused

on the inheritance of functional asymmetry (particularly handedness) (Annett, 1985; McManus, 1985), few have explored the contribution of the environment (Yeo and Gangestad, 1993). One rarely explored source of influence on functional brain asymmetry is environmental variations during early development (Denenberg, 1978; Rogers, 1982; Tang et al., 2003).

In the rat, postnatal handling (Levine, 1960), a procedure that involves daily brief separation of the pups from their mother, handling by the experimenter, and exposure of the pups to a novel environment, was first shown to induce functional asymmetry in the neocortex of the rat (Denenberg, 1978). Neonatal novelty exposure, a procedure similar to postnatal handling but involving only the exposure to a novel environment, leads to modification of hippocampal volumetric asymmetry (Verstynen et al., 2001). Therefore, the early experience-induced changes in brain asymmetry are not only expressed in the evolutionarily recent neocortex but also in the evolutionarily ancient hippocampus. At the level of behavior, these changes in anatomical brain asymmetry are also accompanied by a shift in paw preference in a reaching task (Tang and Verstynen, 2002) and in turning direction preference during the exploration of an unfamiliar environment (Tang et al., 2003; Tang and Reeb, 2004). Interestingly, early experience of differential nutrition did not affect asymmetry in hippocampal cell counts (Lister et al., 2006).

In the present study, we investigated possible asymmetry in synaptic plasticity of the male rat hippocampus induced by neonatal novelty exposure. Male pups were pseudo-randomly assigned within a litter to the Novel and Home groups, with their body sizes balanced between the two groups. Female pups were only included to help make up a constant litter size of eight for all litters. Neonatal novelty exposure was performed daily in the housing room between 11 AM and 3 PM on postnatal days 1–21. The dam was first removed from the home cage and kept in a holding cage. Then Novel pups were individually transferred to their own clean nonhome cages (28 × 16 × 13 cm³) lined with fresh bedding similar to that in the

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home cage. After spending 3 min in the new cage, the Novel pups were returned to the home cage in which the Home pups remained. Each Novel pup was yoked to a Home pup—each time a Novel pup was picked up during the transfer between the home and novel cage, the yoked Home pup was also picked up similarly but placed back into the home cage. After the Novel and Home pups were reunited in the home cage, the dam was then returned to the home cage.

This experimental design ensures that Novel and Home pups do not differ in their separation from their mothers nor do they differ in the amount of experimenter touch received. The only difference is the exposure of the Novel pups to a relatively novel nonhome environment. This epigenetic manipulation has been demonstrated to increase hippocampal plasticity (Tang and Zou, 2002) and corticosterone modulation of plasticity (Zou et al., 2001), to modify behavioral (Tang and Verstynen, 2002; Tang and Reeb, 2004; Tang et al., 2006) and anatomical asymmetry (Verstynen et al., 2001), and to enhance social (Tang et al., 2003) and spatial memory (Tang, 2001; Tang et al., 2006) during adulthood.

When rats reached mid-adulthood (7–8 months of age), electrophysiology experiments were carried out *in vitro* to assess synaptic plasticity. As the stress of moving a rat to a new environment immediately prior to the recording can affect LTP (Xu et al., 1998), the experimenter followed a strict transfer protocol involving the same transfer time and route (<1 min and <30 m). Because the circadian rhythm in the circulating corticosterone concentration can also affect LTP (de Kloet et al., 1999), rats were always euthanized at ~11 AM to minimize this source variance. To minimize the chance that the background stress (e.g. facility maintenance activities) would confound the Novel–Home differences, the order of slice experiments was counterbalanced between Novel and Home rats with one Novel and one Home recorded on consecutive days. Most critical to the study of asymmetry, special care was given to insure that potential left–right differences were not due to any systematic differential treatment of the left and right slices. First, hippocampal slices from both the left and right sides were cut simultaneously in a single block of tissue with the neocortex attached. Second, within each day, the order of recording the left and right slices was counterbalanced to avoid potential confounding effects due to differential decline of slice health.

After being deeply anesthetized with halothane, rats were decapitated and the brain was quickly removed and placed in ice cold artificial cerebrospinal fluid (ACSF) that was continuously oxygenated with 5% CO₂/95% O₂. The composition of ACSF was as follows (in mM): NaCl 124.0; KCl 2.5; KHPO₄ 1.2; CaCl₂ 2.4; MgSO₄ 1.3; NaHCO₃ 26, and glucose 10. Coronal slices (400- μ m thick) were cut using a 752M-vibroslice (Campden Instruments) and incubated at room temperature in continuously oxygenated ACSF for at least 1 h. For recording, slices were transferred to a standard submerging chamber (Medical System Corporation) and continuously perfused with oxygenated ACSF at 32°C. A concentric bipolar stimulating electrode was placed in the CA1 stratum radiatum and con-

stant current pulses (0.1–0.2 mA, 0.2-ms duration) were delivered at 0.1 Hz. Field EPSPs were recorded in the CA1 stratum radiatum using a glass microelectrode filled with 3 M NaCl (resistance: 1–3 M Ω). Signals were band-pass filtered (3 Hz–3 KHz), digitized, and stored in a computer with custom-made LabView (National Instrument) programs. Data were collected within 10 h from dissection.

An input/output function was obtained using test pulses at 16 different intensity levels ranging from minimum intensity to generate a detectable response to the intensity required for evoking the maximum EPSP amplitude. The intensity of the test pulse was set at half the intensity that first induced population spikes and stability of the field potential was established for 10 min before LTP induction. The experiment was continued only if the field EPSP amplitudes were stable for at least 10 min, after which high-frequency stimulation (HFS, 10 trains of 20 stimuli at 200 Hz at 2-s intervals at the intensity of the test stimuli (Pavlidis et al., 1996) was applied. Field EPSP recordings were resumed and continued for a minimum of 30 min using test pulses at the pre-HFS setting. This minimum recording time allowed more slices to be recorded from a given animal, thus improving the reliability of the estimated EPSP potentiation from each of two hippocampi within each rat.

Overall main effects of novelty exposure on LTP, irrespective of the side of the hippocampus, have been previously reported in Tang and Zou (2002). In the current study, by analyzing a subgroup of these rats of which EPSPs were successfully recorded from both the left and right hippocampal slices, we specifically examined whether neonatal novelty exposure has an asymmetric effect on several forms of hippocampal synaptic plasticity associated with different phases after the HFS. Statistical analysis was performed using both the individual animal and the individual slice as the units of analysis. Because converging results from the two types of analysis may help increase our confidence in the data, results from both analyses are presented. For animal-based analysis, data from multiple slices were averaged for the left and right sides separately to form a left and right measure for each individual rat.

Potentiation of the extracellularly-recorded excitatory postsynaptic potentials (fEPSPs) in the CA1 of the adult left and right hippocampi was assessed *in vitro* in a total of 43 slices from 8 animals (4 Novel) born to 2 dams (Fig. 1a) following standard procedures (Fig. 1b). Stimulating the fibers of the Schaffer collaterals elicited fEPSPs at the proximal dendrites of the CA1, which were potentiated by HFS (Fig. 1c). Amplitude of the field potential during the 10 min immediately before high frequency stimulation did not differ significantly between the Novel and Home rats, nor did it differ between the left and right hippocampi (we computed correlations between baseline amplitude and all subsequent plasticity measures and found that none of the correlations for either side was significant) (animal-based: $p_s > 0.20$; slice-based: $p_s > 0.20$) (Table 1). Nor was the novelty \times side interaction found significant (animal-based: $p > 0.20$; slice-based: $p > 0.20$). Figure 1d,e show amplitude of the EPSPs during 10 min before and

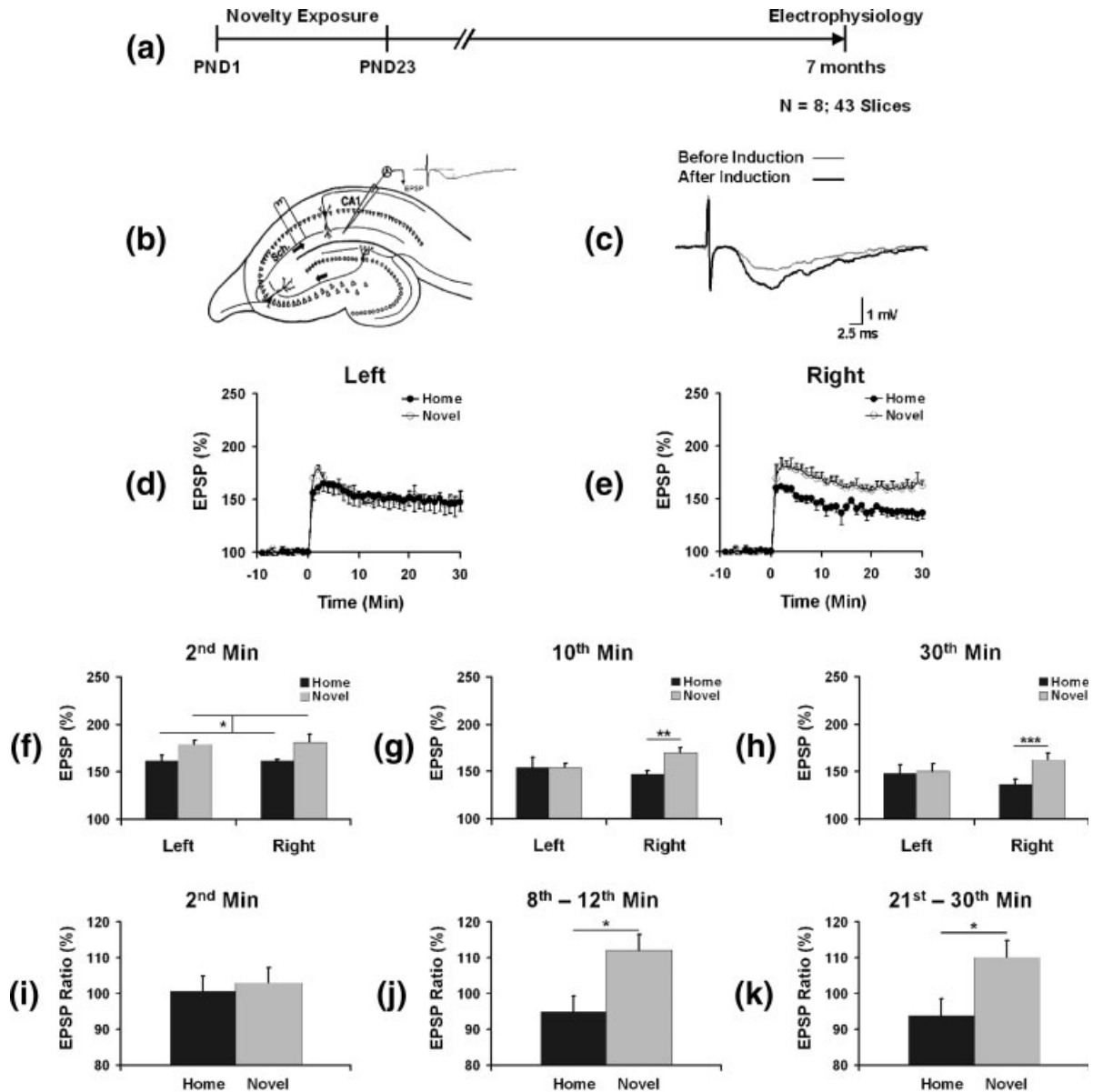


FIGURE 1. Neonatal novelty exposure selectively enhances longer-lasting forms of synaptic plasticity in the right hippocampus of the adult male rat. (a) Timeline of experiment. (b) Placement of the stimulation and recording electrodes. (c) An example of a potentiated EPSP relative to baseline. (d,e) A right-sided phase-specific neonatal novelty effect on potentiation of EPSPs. (f-h) This asymmetric Novelty effect is time-dependent with a

symmetric effect on PTP measured at the 2nd minute (f) but a right-sided enhancement on STP at the 10th minute (g) and LTP at the 30th minute (h). (i-k) Right/Left ratio in STP (j, 8–12th minute average) and LTP (k, 21st–30th minute average) but not PTP are selectively modulated by neonatal novelty exposure (i, 2nd minute). * $p < 0.05$; ** $p < 0.025$; *** $p < 0.005$.

30 min following the HFS for the left and right slices respectively, with each data point an average of six successive trials expressed in percentage of baseline amplitude.

The amplitude of EPSPs during the entire 30 min after HFS was analyzed to capture phase-specific patterns of potentiation. We found a significant novelty \times side \times time interaction effect [Fig. 1d,e: animal-based cubic trend: $F_{1,6} = 13.14$, $p < 0.001$, $f = 1.48$; slice-based-cubic trend: $F_{1,39} = 5.70$, $p < 0.025$, $f = 0.36$] which indicates an experience-dependent and phase-specific asymmetry in EPSP potentiation. We performed fur-

ther follow-up tests on EPSP potentiation at the 2nd, 10th, and 30th minutes to measure PTP, STP, and LTP respectively (Stevens et al., 1994). During the initial brief phase of the potentiation, the effect of novelty exposure on PTP (measured at 2nd minute), was symmetric (Fig. 1f), with Novel showing greater potentiation than Home in both the left and right slices [novelty main effect: animal-based, $F_{1,6} = 7.01$, $p < 0.05$, $f = 1.08$; slice-based: $F_{1,39} = 12.11$, $p < 0.005$, $f = 0.56$]. In contrast, during the later phase of the potentiation, the novelty effect on both STP and LTP (measured at the 10th and 30th

TABLE 1.

Baseline fEPSP Amplitudes (mV)

	Left	Right
Novel	0.86 ± 0.04 mV	0.92 ± 0.04 mV
Home	0.91 ± 0.04 mV	0.89 ± 0.04 mV

Results presented in mean ± sem.

minute, respectively), was asymmetric, observed only in the right hippocampal slices [Fig. 1g,h; 10th minute/animal-based: $t_6 = -3.15$, $p < 0.02$, Cohen's $d = 2.57$; 10th minute/slice based: $t_{18} = -3.13$, $p < 0.01$, Cohen's $d = 1.48$; 30th min/animal-based: $t_6 = -3.35$; $p < 0.02$; Cohen's $d = 2.73$; 30th min/slice based: $t_{18} = -3.53$; $p < 0.005$; Cohen's $d = 1.67$] (preliminary analysis of the LTP portion was previously reported in a book chapter (Tang, 2003)). Thus, the asymmetric effect of neonatal novelty exposure is specific to the longer-lasting forms of synaptic plasticity.

To further confirm these findings, we computed ratios of the right-to-left measures using the individual rat as the unit of analysis. Parallel to the above analyses, we found a significant time × novelty interaction on the R/L ratio of EPSP amplitude (cubic trend: $F(1,6) = 13.39$, $p < 0.025$, $f = 1.49$), suggesting that neonatal novelty exposure affects the R/L ratio in a time-dependent manner. To further examine the time dependency, we performed follow-up tests for PTP, STP, and LTP. Because ratios are noisier than the original raw amplitude measure, we performed comparisons on averages of minutes 8–12 and 21–30 for STP and LTP, respectively. Consistent with earlier analyses, while the main novelty effect on PTP R/L ratios was not significant (Fig. 1i, 2nd min: $p > 0.20$), novelty effects on the STP and LTP R/L ratios were significant (Fig. 1j,k: average minute 8–12: $F(1,6) = 7.27$, $p < 0.05$, $f = 1.10$; average minute 21–30: $F(1,6) = 6.158$, $p < 0.05$, $f = 1.01$; Fig. 1k). Therefore, this ratio analysis further confirms the finding that neonatal novelty exposure selectively affects asymmetry in STP and LTP, the longer-lasting forms of synaptic plasticity, but not the short-lasting PTP. It should be noted that effect sizes Cohen's d and f reported here are large or near-large (Rosenthal and Rosnow, 1984).

An elegant study in mice (Kawakami et al., 2003) showed that LTP asymmetry can be found after cutting connections between the left and right hippocampi. The present findings demonstrate that LTP asymmetry can emerge naturally as a result of rather subtle differences in early life environment. Because the genetic makeup does not differ systematically between the Novel and Home pups within the same litters, we are able to conclude that this right-sided increase in longer-lasting forms of hippocampal plasticity is epigenetically induced and that early life environmental differences constitute one possible developmental origin of asymmetry in hippocampal synaptic plasticity.

It is important to clarify that while the observed novelty effects on STP and LTP indicate that experience can give rise

to this expression of asymmetry, these data do not address the issue of whether asymmetry in synaptic plasticity is innate. Observations of asymmetry in adulthood (e.g., LaMendola and Bever, 1997) do not necessarily imply innateness of such asymmetry (here, we assume innateness refers to being present at birth) because asymmetry found at the time of observation could still be dependent upon other factors, such as the animals' prior experience (as we are showing here), strain (e.g., Collins, 1981) or sex (e.g., Akers et al., 2004).

Because the current sample size is relatively small, one could argue that it is not possible to rule out the possibility that the distribution of R/L ratio is bimodal. A change from the current continuous variable to a binary variable would reduce the statistical power, making the current findings statistically less significant. Indeed, measures of asymmetry in rodents appeared to have two general classes of distributions, one is continuous as in the case of left-right turning preference (Tang and Reeb, 2004) and the other discrete as in the case of paw preference in a reaching task (Tang and Verstynen, 2002). It is our belief that the asymmetries in STP and LTP are most likely a continuous variable because, unlike the case of paw preference where only one paw was allowed and measured as an all or none response, both the left and right hippocampi showed varying degrees of evoked field potential response to the testing pulses. Nevertheless, to increase the strength of the generality, future experiments should examine this STP/LTP selective asymmetric effect with a greater sample size.

If a between-litter design is used, as in the case of early handling studies, a small litter number may confound the manipulation effect. Here the novelty exposure was a within-litter effect (crossed), thus cannot be confounded by a litter effect. For the purpose of confirming generality of the present finding, this design advantage does not change the need for future studies using a larger number of litters. Furthermore, given many reported sex differences in early stimulation effects (briefly reviewed in Akers et al. (2004)), it remains to be investigated whether a different pattern of asymmetry exists between the two female hippocampi.

Subsequent events following the novelty exposures, e.g. a possible increase in maternal care toward the novelty-exposed pups might contribute to the asymmetric increase in STP/LTP. However, recent studies of differential maternal care towards the novelty-exposed and home-staying pups revealed that despite reduced maternal care being received, the novelty-exposed adult offspring showed relative enhancement in multiple cognitive, social, and neuroendocrine functions (Tang et al., 2006). Therefore, greater maternal care is unlikely to be the mediator of the wide range of previously reported novelty-exposure effects. Because all studies of early life intervention effects on adult function necessitate a prolonged delay between the initial manipulation and the adult assessment, we believe that the initial immediate effects on the pups behavior and physiology must lead to further changes in the pups' effective social and physical environment, which in turn can further contribute to differences in adulthood.

Different from typical studies of synaptic plasticity that focus on very long-lasting changes (LTP), we analyzed the minute-

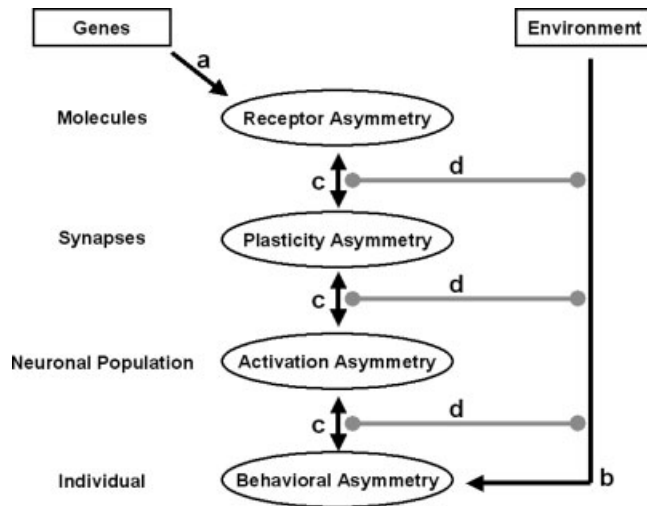


FIGURE 2. A conceptual framework offering a dynamic account for the development of brain and functional asymmetry across multiple levels of organization. (a) Genetics determine the initial asymmetry at the molecular level. (b) Environment affects behavioral asymmetry. (c) Dynamic interactions occur between multiple levels of organizations. (d) As a result of interaction among (a) through (c), environmental inputs enable and amplify the initial asymmetry at the molecular level to be expressed at multiple higher levels of organization. The end result is an experience-dependent induction and amplification of behavioral asymmetry through development.

by-minute changes in HFS induced potentiation of EPSPs throughout 30 min of observation to contrast the immediate change in EPSP amplitude with the later longer-lasting changes. We found that in male rats the asymmetric effects of neonatal novelty exposure on EPSP potentiation is phase-specific, with the initial effect being a bilateral increase and the later effects being a selective right-sided increase in EPSP amplitude. This phase-specificity suggests that the asymmetry in hippocampal plasticity may have less to do with the immediate information processing after an experience but more to do with the long-term storage of this experience.

To consider how this hippocampal asymmetry in memory-related mechanisms might contribute to cortically and behaviorally expressed functional asymmetry, we propose a process-based developmental framework (Fig. 2) which assumes that (1) genetics plays a role in setting up an initial small asymmetry in the density of receptors that contribute selectively to the long-lasting forms of synaptic plasticity (Fig. 2a); (2) dynamic interactions occur between the individual and its environment (Fig. 2b) as well as between levels of organizations (Fig. 2c); (3) through these interactions, environmental influences enable and facilitate the functional expressions of the receptor asymmetry at the levels of synaptic plasticity, activation of neuronal populations, and behavior (Fig. 2d).

From a computational point of view, a greater STP and LTP mean a greater rate of learning, which has been shown as one of the network properties critical for the development of functional lateralization in neural network models (Reggia et al., 1998). An initial asymmetry in hippocampal synaptic plasticity,

even if very small, may serve to “break” the symmetry, providing differential rates of task acquisition between the two hippocampi during development, leading to asymmetric task-related activation. Because the neocortex and the hippocampus are reciprocally interconnected (see review in Rolls, 2000) and their electrical activity are coupled (Fell et al., 2007), an asymmetry in hippocampal activation may lead to an asymmetric transfer of a new function to the neocortex.

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