Effective EEG Connectivity Analysis of Episodic Memory Retrieval

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Abstract

Episodic memory formation is associated with large-scale neuronal activity distributed across the cortex. Decades of neuroimaging and patient lesion studies demonstrated the correlation between the roles of specific brain structures in episodic memory retrieval. Distributed, coordinated and synchronized activities across brain regions have also been investigated. However, neuronal mechanisms based on effective connectivity underlying the coordination of this anatomically distributed information processing into introspectively coherent cognition have remained largely unknown. Here we investigate the information flow network of the human brain during episodic memory retrieval. We have estimated local oscillation amplitudes and asymmetric inter-areal synchronization from EEG recordings in individual cortical anatomy by using source reconstruction techniques and effective connectivity methods during episodic memory retrieval. The strength and spectro-anatomical patterns of these inter-areal interactions in sub-second time-scales reveal that the episodic memory retrieval involves the increase of information flow and densely interconnected networks between the prefrontal cortex, the medial temporal lobe, and some subregions of the parietal cortex. In this network, interestingly, the SFG acted as a hub, globally interconnected across broad brain regions.

Keywords: Episodic memory retrieval; Information flow; Effective connectivity; EEG, Memory retrieval network.

Introduction

The next step in the progression of neuroscience is building neuro-cognitive models that describe the dynamics and interaction patterns of brain regions on a macroscopic scale. Indeed, recent advances in cognitive neuroscience have focused on the role of inter-areal interactions between various specialized brain regions and functional connectivity in human cognition (Stevens, 2009; Yarkoni et al., 2010, Park & Friston, 2013).

The study of human brain connectivity generally falls under three categories: structural, functional, and effective connectivity (Bullmore & Sporns, 2009). Structural connectivity refers to the static anatomical structure of the brain. This can be studied *in vivo* using invasive axonal labeling techniques, magnetic resonance imaging (MRI, Lauterbur, 1973) or diffusion tensor imaging (Moseley et al.,

1990) devices. Both functional and effective connectivity are defined with respect to a cognitive task and denote synchronized activity of two neuroanatomical regions during task execution. However, effective connectivity is able to deal with asymmetric or causal dependencies between the two regions, while functional connectivity has only a symmetrical nature. Thus, the term "information flow" is often used to indicate directionally specific effective connectivity between two brain structures. Dynamic causal modeling (DCM), structural equation modeling (SEM), transfer entropy, and Granger-causal methods are popular effective connectivity methods and they can be applied to functional MRI (fMRI) and/or electrophysiological imaging data such as electroencephalography (EEG), intracranial EEG (iEEG), and magnetoencephalography (MEG).

Episodic memory formation is a complex neurocognitive process that is associated with large-scale neuronal activity distributed across the cortex. However, neuronal mechanisms based on the effective connectivity underlying the coordination of this anatomically distributed processing have remained largely unknown.

Decades of neuroimaging and patient lesion studies correlated the roles of specific brain regions to episodic memory retrieval such as the prefrontal cortex (Blumenfeld & Ranganath, 2007; Duarte et al., 2005), the medial temporal lobe (Eichenbaum et al., 2007; Mitchell & Johnson, 2009; Squire et al., 2004; Simons & Spiers, 2003; Vargha-Kadem et al., 1997) and some subregions of the parietal cortex (Hutchinson et al., 2009; Spaniol et al., 2009; Vilberg & Rugg, 2008).

Furthermore, distributed and coordinated activities across brain regions are regarded to be important to the memory retrieval processes (Buzsáki, 1996; Eichenbaum, 2000; McClelland et al., 1995; Nadel & Moscovitch, 1997; Norman & O'Reilly, 2003; Teyler & DiScenna, 1986). Synchronized activity in the local field potential (LFP) is also related to coordinating these processes (Fell & Axmacher, 2011).

Recently, following these previous findings, frequency multiplexing of brain regions involved in episodic memory retrieval (Watrous et al., 2013) have also been studied, but effective connectivity has not yet been considered.

Here in this paper, we are primarily concerned with the information flow network of the human brain during

episodic memory retrieval. We have estimated local oscillation amplitudes and asymmetric inter-areal synchronization from EEG recordings in individual cortical anatomy by using source reconstruction techniques and the effective connectivity method during episodic memory retrieval.

Materials and Methods

Participants and electrophysiology setup

Eight neurologically healthy participants (mean age, 24.3 ± 2.7 years; 4 women) gave informed consent, which was approved by the institutional review board (IRB) at the Clinical Research Institute of Seoul National University Hospital for the protection of human subjects. Electrophysiological methods and electrode localization were similar to those described previously (Lee et al., 2012). In brief, participants wore a cap equipped with 128 Ag/AgCl electrodes. Eye movements and blinks were monitored by horizontal and vertical electrooculography signals. Impedance was maintained at 5–10 kΩ or less. EEG signals were sampled at 1,000 Hz/channel using a Neuroscan SynAmps amplifier (Neuroscan, El Paso, TX). Signals were referenced to a common average consisting of a ground and reference electrodes over frontal and lateral temporal areas to minimize the effect of the referencing scheme on synchronization measures (Nunez & Srinivasan, 2006). Recordings were then imported into MATLAB (MathWorks, Natick, MA) for analyses.

Behavioral task

Participants play a memory recall game depicted in Figure 1. The game consists of two sessions which naturally lead a participant to remember and recall several episodic memories. The game begins with a tutorial composed of a concise example set of whole tasks in order to allow the participant to become accustomed to the game environment. Following the tutorial, the memory encoding session starts
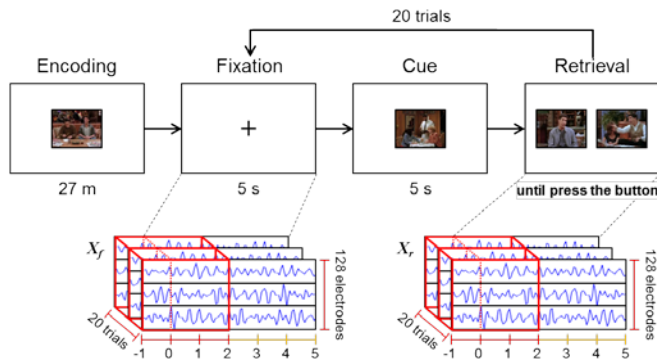
Figure 1: Experimental setup and EEG acquisition. EEG signals are recorded during 20 trials of the retrieval session in the memory recall game and extracted for fixation and retrieval query tasks from 1 second before to 2 seconds after the onset of each task throughout 128 electrodes.

and the participant watches an episode of a television sitcom for 27 minutes. The spoken language in the movie is American English, and subtitles are not displayed. After watching the movie for memory acquisition, the participant continues to perform 20 rounds of the memory retrieval session. First, the participant stares at a cross in the center of the screen during the fixation task. Then, the participant is provided with a video clip of the movie as a retrieval cue. During the retrieval task, two still images captured in the following scene from the retrieval cue in a random order are presented. The participant is asked to decide whether the order of the two images is correct or incorrect using a small keypad.

Preprocessing and source reconstruction

All analyses used EEGLAB (Delorme & Makeig, 2004), SIFT (Mullen et al., 2010, Delorme et al., 2011) and custom-written codes in MATLAB. Raw EEG signals from the memory recall game were extracted for both the fixation and retrieval query tasks from 1 second before to 2 seconds following each task. Our primary behavioral contrast was retrieval versus fixation (non-retrieval).

Following FIR band-pass filtering between 2.0 and 50.0 Hz to exclude unnecessary frequencies, EEG signals were subjected to the independent component analysis (ICA). A dual symmetric equivalent dipole model was then fit to each source signal using EEGLAB's Dipfit2 plugin with a four-shell spherical head model.

Effective connectivity estimation

Information flows between inter-areal sources of EEG were measured by computing the direct directed transfer function (dDTF, Korzeniewska et al., 2003) for each pair of source signals. The dDTF is measure of direct information transfer among brain structures on the basis of LFP. First, the directed transfer function (DTF) is formulated in the framework of a multivariate autoregressive (MVAR) model fitted to the EEG signal. The MVAR model is expressed as:

$$X(t) = \sum_{m=1}^{p} C(m)X(t-m) + E(t) , \qquad (1)$$

where $X(t)$ is a vector of k EEG signals recorded in time t, $E(t)$ is the vector of multivariate uncorrelated white noise process, $C(m)$ are the $k \times k$ matrices of model coefficients, and p is the model order. The model order is determined by means of criteria such as Akaike information criterion, Schwarz-Bayes criterion, the final prediction error criterion, Hannan-Quinn criterion (Lütkepohl, 2006).

In order to investigate the spectral properties between the signals, the Fourier transformation is applied to (1) where the transform functions are of the form:

$$X(f) = Y(f)E(f), \qquad (2)$$

where f denotes frequency, $Y(f) = \left(\sum_{m=1}^{p} C(m)e^{-i2\pi f \Delta t} \right)^{-1}$.

DTF is usually normalized with respect to the inflows of the activity so after normalization it takes the form:

$$\gamma_{ij}^2(f) = \frac{|Y_{ij}(f)|^2}{\sum_{n=1}^k |Y_{in}(f)|^2} \qquad (3)$$

However, the full frequency DTF (ffDTF, Korzeniewska et al., 2003) uses another procedure of normalization expressed as (4), so that its spectral properties depend only on the outflow of that channel, not on the frequency:

$$\eta_{ij}^2(f) = \frac{|Y_{ij}(f)|^2}{\sum_f \sum_{n=1}^k |Y_{in}(f)|^2} \qquad (4)$$

Power spectrum S and the partial coherence (pCoh) χ_{ij}^2 can be easily calculated with this multivariate approach using (5) and (6):

$$S(f) = Y(f)VY^*(f), \qquad (5)$$

where V is the variance of the $E(f)$, the asterisk (*) stands for conjugate transpose.

$$\chi_{ij}^2(f) = \frac{R_{ij}^2(f)}{R_{ii}(f)R_{jj}(f)}, \qquad (6)$$

where $R_{ij}(f)$ is the minor produced by removing the i–th row and the j–th column from the power spectrum matrix S.

Consequently, the dDTF can be derived by the product of the ffDTF and the pCoh:

$$\delta_{ij}(f) = \chi_{ij}(f)\,\eta_{ij}(f) \qquad (7)$$

Here, δ_{ij} defines the connection between the i–th input and the j–th output of the system. It takes values in the interval [0, 1] where a value close to 1 means a consistent information flow in the direction $j \rightarrow i$, and a value close to 0 indicates little or no information flow.

Experimental Results

Active brain regions during retrieval

The time-varying dDTF estimates were obtained by using a sliding-window MVAR model with a 500 ms window length and 10 ms step size producing 251 time points. The dDTF is integrated over the frequency band between 2 and 50 Hz.

The dDTF evaluation revealed prominent information flow increases between frontal cortex (superior frontal gyrus, SFG; middle frontal gyrus, MFG; inferior frontal gyrus, IFG; prefrontal cortex, PFC), and specific subregions of medial temporal (hypothalamus, HYP; thalamus, THA; medial temporal lobe, MTL), parietal (precuneus, PCN; inferior parietal lobe, IPL) and occipital (primary visual cortex, PVC) regions when participants retrieved the episodic memory from the memory recall game. The importance of these regions in episodic memory retrieval is consistent with those established through previous decades of work (Blumenfeld & Ranganath, 2007; Mitchell & Johnson, 2009; Hutchinson et al., 2009; and so on). Thus, we restricted subsequent
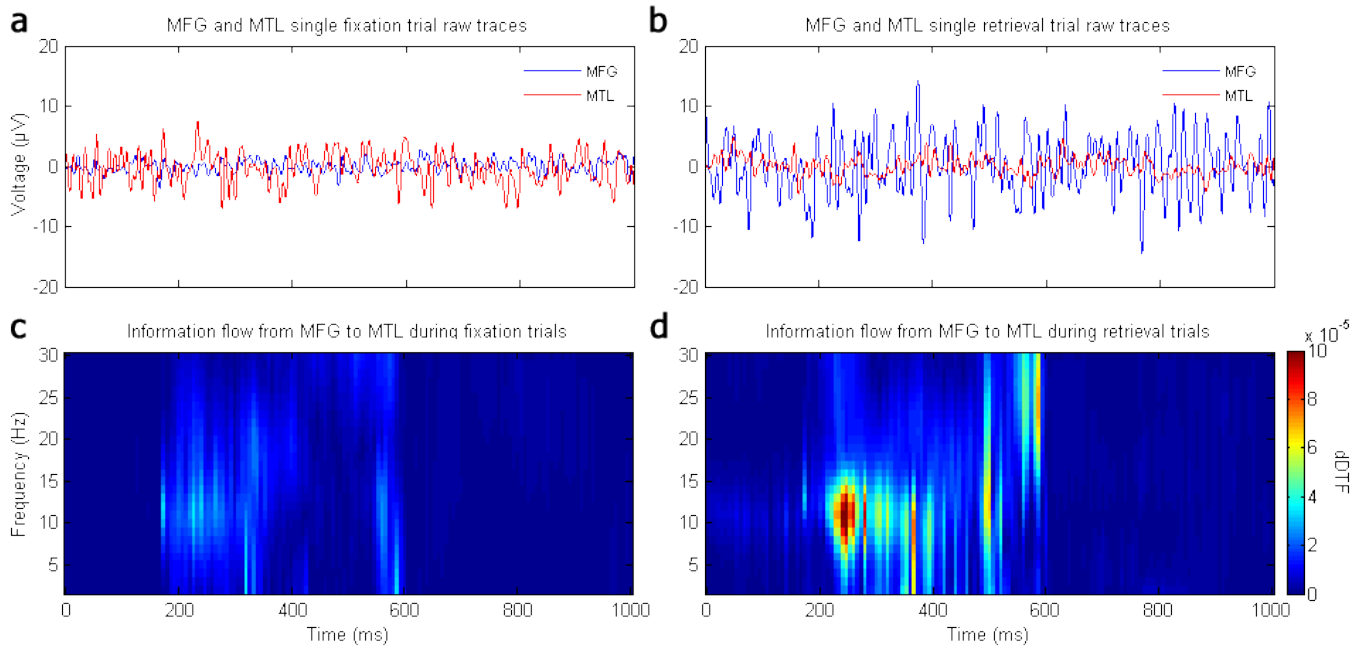
Figure 2: Examples of the information flow captured from MFG-MTL during fixation and retrieval tasks. **(a, b)** Raw EEG traces of MFG and MTL recorded from a participant during single trial of fixation and retrieval tasks. The *x* axis corresponds to time that shown in **c** and **d**. **(c, d)** Information flow from MFG to MTL measured by dDTF across all MFG and MTL pairs.
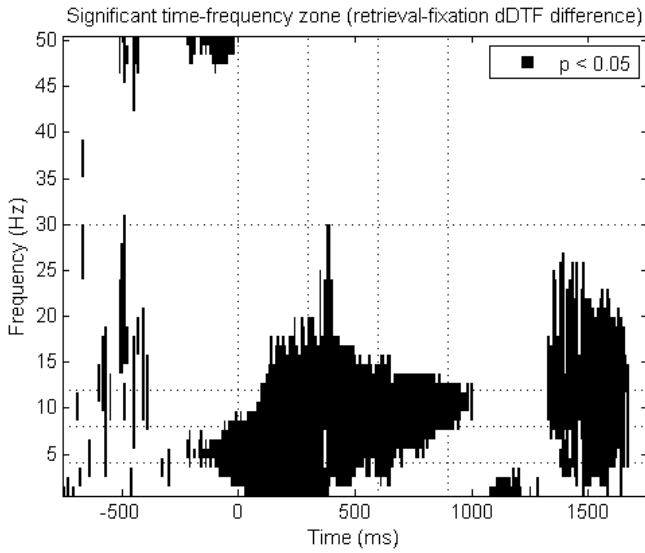
Figure 3: Significant time-frequency zone. Black areas indicate that the dDTF values are significantly different ($p_{t\text{-}test} < 0.05$) between fixation and retrieval. Dashed lines indicate our interesting boundaries of time and frequency (time: 0, 300, 600, 900 ms; frequency: 4, 8, 12, 30 Hz).

analyses to the information flow of 90 source signal pairs consisting of these ten active brain regions.

Increased information flow from MFG to MTL was visually evident in a lower frequency band (2–15 Hz) during retrieval tasks compared with fixation as shown in Figure 2 (c, d). Individual raw EEG traces also revealed that oscillatory powers of MFG typically increased following the retrieval tasks as shown in Figure 2 (a, b), however, these individual changes could not describe the specific direction of the interregional information flow.

Significant time-frequency zone

To clarify the active information flows associated with specific frequency and time bands, we found time-frequency areas showing significantly different dDTF between fixation and retrieval tasks. Each of differences between dDTF values of fixation and retrieval is tested by the two sample t-test with fixed time and frequency. As shown in Figure 3, time ranges between 0–1000 ms and frequency ranges between 2–30 Hz showed significant differences ($p_{t\text{-}test} < 0.05$). Differences around 1500 ms were significant as well, but this time band was not considered as an analysis target because it was too delayed from the onset of stimuli and could be caused by irrelative facts.

Information flow increases in active brain regions

The estimated information flow between the 90 active brain region pairs in the preferred frequencies (4 and 8 Hz) and time band (0–1000 ms) are depicted in Figure 4 (a, b). We found statistically meaningful increases in most of the pairs during retrieval tasks ($p_{t\text{-}test} < 0.05$, 76 pairs in 4 Hz and 80 pairs in 8 Hz).
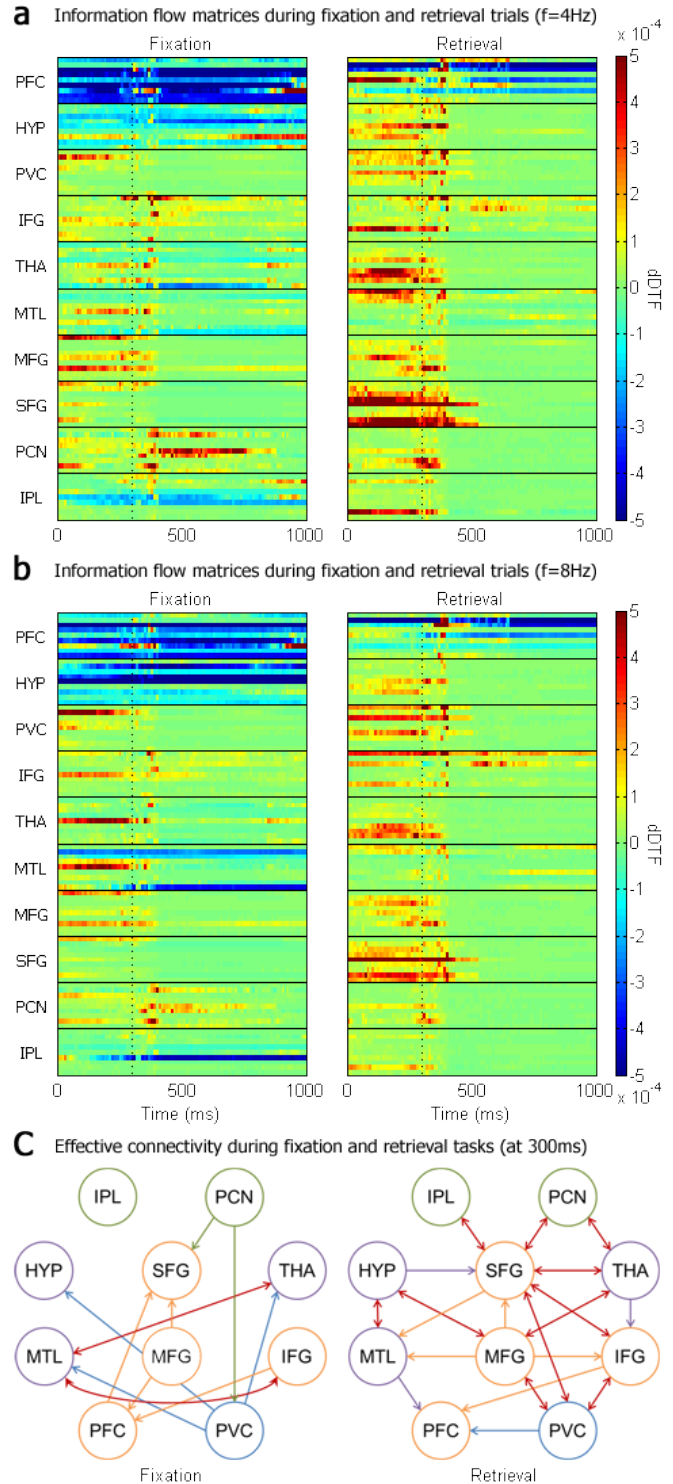
Figure 4: Information flows between brain regions and networks of the effective connectivity during fixation and retrieval tasks. **(a)** Information flow matrices in 4 Hz frequency. Each labeled line block consists of 10 pairs from the labeled region and the same order. Red color indicates high information flow. **(b)** Information flow matrices in 8 Hz frequency. **(c)** Effective connectivity network during fixation and retrieval at 300 ms (dashed vertical lines in **a, b**).

To evaluate topological interactions across the brain regions, we adopted a graph theoretic approach. We treated each brain region as a node in a network that was functionally connected considering its directions via dDTF at a given time (300 ms) and frequency (2–30 Hz) as seen in Figure 4 (c). We found a densely interconnected network during retrieval while fixation had only sparse local networks in the frontal and occipital-medial temporal area. Importantly, there were a number of asymmetries regarding the estimated information flow between brain regions (e.g. MFG → MTL; MTL → PFC).

While overall increases in connectivity across the network during memory retrieval were observed, specific brain region such as SFG acted as a hub. SFG showed global connectivity with overall brain regions.

Discussion and Conclusion

We sought to determine the effective network interactions among brain regions that have been implicated in episodic memory retrieval. We estimated information flows from EEG signals recorded during tasks of a memory recall game. A source reconstruction technique was used for estimating the activity of the neuronal sources generating the sensor level data, attenuating the problem of field spread. To measure the effective connectivity, the dDTF method based on an MVAR model was adopted in order to calculate directed causal relations between source signals and to deal with short epochs of EEG activities.

We revealed that episodic memory retrieval could be characterized by increase of information flows between the prefrontal cortex, medial temporal lobe, and the parietal cortex, along with the globally interconnected effective connectivity network of them across the 2–30 Hz frequency band. Interestingly, SFG acted as a hub in the network during memory retrieval. Because SFG is a key component of the neural network of memory process and the participation of this region in memory process is triggered by the highest level of executive processing (Boisgueheneuc et al., 2006), these findings could be consistent with many decades of work that point to the importance of SFG in episodic memory retrieval task.

Our results also emphasize asymmetric information flows between brain regions. To the best of our knowledge, this has not been studied previously with non-invasive human brain signal recordings. We found a meaningful result regarding this matter, related to the information flows of parietal cortex. The parietal cortex is one of the regions that is most frequently activated during episodic-memory retrieval. Our effective connectivity analysis showed the information flow of the superior parietal regions (PCN) and PVC are significantly changed. During the retrieval task, the information flow is activated from SFG to PCN that is inverse direction of the non-retrieval task. This result could partially support the dual process model of attention to memory (Cabeza, 2008), which presented the superior parietal cortex is associated with top-down processes that support retrieval search, monitoring and verification.

Overall, our study provides a new perspective on how the human brain processes episodic memory retrieval. By employing effective EEG connectivity and a graph theoretic approach, our results could support episodic memory retrieval models that emphasize globally dense network and time-frequency-specific effective connectivity, rather than regionally mediated activity alone or an undirected functional connectivity.

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