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Theta oscillations support the interface between language and memory

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ABSTRACT

Recent evidence shows that hippocampal theta oscillations, usually linked to memory and navigation, are also observed during online language processing, suggesting a shared neurophysiological mechanism between language and memory. However, it remains to be established what specific roles hippocampal theta oscillations may play in language, and whether and how theta mediates the communication between the hippocampus and the perisylvian cortical areas, generally thought to support language processing. With whole-head magneto-encephalographic (MEG) recordings, the present study investigated these questions with two experiments. Using a violation paradigm, extensively used for studying neural underpinnings of different aspects of linguistic processing, we found increased theta power (4–8 Hz) in the hippocampal formation, when participants read a semantically incorrect vs. correct sentence ending. Such a pattern of results was replicated using different sentence stimuli in another cohort of participants. Importantly, no significant hippocampal theta power increase was found when participants read a semantically correct but syntactically incorrect sentence ending vs. a correct sentence ending. These findings may suggest that hippocampal theta oscillations are specifically linked to lexical-semantic related processing, and not general information processing in sentence reading. Furthermore, we found significantly transient theta phase coupling between the hippocampus and the left superior temporal gyrus, a hub area of the cortical network for language comprehension. This transient theta phase coupling may provide an important channel that links the memory and language systems for the generation of sentence meaning. Overall, these findings help specify the role of hippocampal theta in language, and provide a novel neurophysiological mechanism at the network level that may support the interface between memory and language.

1. Introduction

The hippocampal formation is critical to spatial navigation and episodic memory (Buzsáki and Tingley, 2018; Lisman et al., 2017), and traditionally has not been linked to language. However, accumulating evidence from human lesion studies (e.g., Duff and Brown-Schmidt, 2012; Klooster, 2016) suggests that the hippocampal formation is important for online language processing, as patients with deficits in this structure exhibit impairment in some aspects of language processing. Using direct recordings from the hippocampal formation in pre-surgical epilepsy patients, Piai et al. (2016) have observed prominent theta oscillations during sentence reading, and that theta power is stronger for sentences of high vs. low context constraints. The finding has revealed for

the first time that hippocampal theta oscillations, which dominate the hippocampal local field potentials during navigation and memory, support language processing as well, and therefore suggest a shared neurophysiological mechanism between memory and language. However, it remains to be established whether hippocampal theta is specifically linked to any particular aspect of linguistic processing, such as semantic processing (Bastiaansen and Hagoort, 2003). Findings from Piai et al. (2016) suggest that hippocampal theta might be associated with semantic but not syntactic processing of language. However, this functional specificity has not been directly tested. Furthermore, language is generally thought to be supported by perisylvian cortical areas. It remains unclear whether theta oscillations coordinate the communication between the hippocampus and perisylvian cortical areas (Covington and

Duff, 2016), a potential mechanism that may link together two usually independently studied systems - memory and language, and enable rapid comprehension during online sentence reading.

The violation paradigm, where researchers perturb an expected element to study how participants react to the violation provides an approach to study the role of hippocampal theta in language. Previous studies have shown that hippocampal theta oscillations can be elicited with the violation paradigm using non-linguistic stimuli, including objects and faces (e.g. Garrido et al., 2015; Gruber et al., 2018); Moreover, this paradigm allows a wide variety of violations and therefore been deployed extensively to study brain activity associated with very specific aspects of linguistic processing (e.g., Friederici, 2002; Kutas and Hillyard, 1984). For example, semantic violations result in a robust N400 event-related potential/magnetic field (ERP/ERF), while syntactic violations are associated with a different ERP (and presumably, processing stage), the P600 (e.g., Mantegna et al., 2019; Muralikrishnan and Idrissi, 2019; Sun et al., 2018). However, ERPs are aggregated neural signals of both low and high frequency bands. It remains unclear what specific frequency band contributes to the observed ERPs. To answer this question, Hagoort et al. (2004) analyzed theta power recorded with electroencephalography (EEG), and have observed enhanced theta power at the EEG sensor level when participants read semantically incorrect vs. correct sentence endings. The authors then speculated that the increased theta power observed at scalp sensors involves contributions from the hippocampus. By using direct recordings from the hippocampus of presurgical patients with intracranial electroencephalography (iEEG), some early studies (e.g., McCarthy et al., 1995) have observed a late negative potential (e.g., peak around 600–800 ms) in the hippocampus elicited by semantically anomalous vs. normal sentence endings. These findings seem to support the notion that the hippocampus plays a role in semantic-related processing speculated in Hagoort et al. (2004). However, it remains to be established whether hippocampal theta supports semantic processing, as well as other aspect of linguistic processing outside of the domain of semantics.

With recent development of source localization techniques, MEG provides an avenue to study deep source activities, including the hippocampus non-invasively in routine experimentations (Pu, Cheyne et al., 2018). By taking advantage of the whole-head MEG recordings and a sophisticated source localization technique, the present project aimed to investigate whether and how hippocampal theta supports online sentence reading with the violation paradigm. We recorded neuromagnetic activities of healthy participants, while they were reading sentences in the MEG scanner. In the first experiment, we visually presented participants with syntactically correct sentences ended with either a semantically correct word or semantically incorrect word. We investiagated whether there was an increase in hippocampal theta power in reading semantically incorrect vs. correct sentence endings, as speculated in Hagoort et al. (2004). In the second experiment, we aimed to first replicate the results from experiment one, and to further investigate whether hippocampal theta oscillations support syntactic processing, a domain outside the domain of the semantics. To this end, in addition to the two sentence types (but different sentences) used in the first experiment, we included sentences ended with a semantically correct but syntactically incorrect word (see Table 1 for the experimental conditions in the two experiments). We compared hippocampal theta power in reading the semantcially incorrect and the syntactically incorrect sentence endings to hippocampal theta power in reading the correct sentence endings respectively. If a prominent theta power change in the hippocampal formation was observed in the experimental modulations above, we further investigated whether canonical language areas in the cortex exhibited similar patterns of theta power change. If yes, we investigated whether theta oscillations coordinated the communication between the hippocampal formation and the neocortical areas. We computed phase-locking value (Lachaux et al., 1999) of the instantaneous theta phase differences between the hippocampal formation and the cortical language areas to quantify the hippocampal-neocortical

interaction.

2. Materials and methods

Participants. Fifteen right-handed participants (females = 8; mean age = 27 years; range = 19–36 years) participated in experiment one. Seventeen right-handed participants (females = 9; mean age = 24 years; range = 18–38 years) participated in experiment two. Additional three participants' data were not included in the analyses in experiment two due to excessive head movement (>4 mm in any direction) or malfunction of the computer. All the participants were native English speakers recruited from Macquarie University and were compensated financially for approximately 1.5 hs of their participation. The participants had normal-to-corrected-to-normal vision. They had no past or present psychiatric disorders, and did not take any psychoactive or hormonal medications at the time of testing (self-report). The two experiments were approved by Macquarie University's human subjects ethics committee. All the participants gave their written informed consent.

Visual displays. Experiments were programmed using Experiment Builder software. Stimuli were projected (InFocus Model IN5108; InFocus, Portland) onto a screen at a viewing distance of about 1.2 m above the participants. Stimuli were presented as black or red letters or shapes at the centre of a light grey background.

3. Stimuli and experimental procedures

Experiment one. One hundred and forty four sentences were drawn from Johnson and Hamm (2000). These stimuli were shown to elicit a robust N400 effect (semantic violation sentence vs. correct sentence) measured by scalp EEG (Johnson and Hamm, 2000). Additional 35 sentences were created to get a total of 179 sentences, in which 90 sentences were correct sentences and 89 sentences were ended with a semantically incorrect word (e.g., 'I take tea with milk and dog'). The length of the sentences varied between four to nine words, but was matched between the two sentence types. Among the 179 sentences, 80 correct and 80 semantically incorrect sentences were presented in the two critical experimental conditions (i.e., correct sentence and semantic violation conditions), 14 (7 for each sentence types) in the filler condition, and 5 in the practice session.

Similar to the experimental protocol in Johnson and Hamm (2000), the onset of a sentence was cued with a display of '#####' for 500 ms, which was followed by a fixation cross (+) for 500 ms before the first word was presented. Each word (except the last one) was presented for 500 ms, followed by a grey screen displayed for 500 ms before the next word was presented. The last word was presented for 900 ms, since increased theta power elicited by the semantic violation condition can last up to more than 800 ms as shown in Hagoort et al. (2004). Increasing the presentation time at the last word would not be a confound, as all the conditions under comparison had the same time length. After the presentation of the last word, a grey screen was presented for 500 ms, which was followed by a display of a black square for 500 ms. The inter-trial-interval (ITI) was randomly jittered between 2700 and 3700 ms (see Fig. 1 for the experimental procedure).

To ensure attention, participants were instructed to look at the screen during sentence presentation, and to press a button using their right hand after the presentation of the black square, if they saw a word in red in

Table 1
Experimental conditions and example sentences.

Experiments	Conditions	Examples
Experiment 1	Semantic violation	The frog ate a **mountain**.
	Correct sentence	The mechanic fixed the **car**.
Experiment 2	Semantic violation	Mary is packing one **mate**.
	Syntactic violation	Mary is packing one **bags**.
	Correct sentence	Mary is packing one **bag**.

occasionally catch trials. We also used an eye tracker to monitor the participants' eyes from a computer display outside the magnetically shielded room (MSR), to ensure that the participants kept their eye open while they were reading the sentences. Sentences were presented to the participants in two blocks and in a random order, with the constraint of a maximum of three consecutive sentences of a given type. Each block lasted about 15–20 min, with two to three minutes' break in between. Before doing the real task, participants did a short practice session to ensure a total understanding of the experimental task.

Experiment two. The task was similar to that in experiment one. Three versions of sentences were presented: e.g., (1) Mary is packing one bag (correct sentence condition); (2) Mary is packing one mate (semantic violation condition); (3) Mary is packing one bags (syntactic violation condition). The stimuli were chosen from Sun et al. (2018), which were shown to elicit robust N400 (semantic violation vs. correct sentence condition) or ELAN and P600 components (syntactic violation vs. correct sentence condition). There were a total of sixty-eight sentences for each condition type in the critical conditions and additional 14 sentences in catch trials (seven for each condition type). All the sentences were presented in two blocks, between which there was a short break. Compared to experiment one, the number of the sentences in each condition in experiment two was slightly less. This was to avoid fatigue and potentially large head movement of the participants due to the elongated experimental time in the MEG scanner. For the same reason, the ITI was decreased to between 2000 ms and 2500 ms (randomly jittered). All the other parameters were the same as those used in experiment one.

MEG data acquisition. Before MEG recording, the positions of three fiducial points (nasion, left and right preauricular), five marker coil positions attached to an elastic cap mounted on the head of the participant and his/her head shape were digitized with a pen digitizer (Polhemus Fastrack, Colchester, VT). Neuromagnetic data were continuously measured using a whole-head MEG system (Model PQ1160R-N2, KIT, Kanazawa, Japan) in a magnetically shielded room (Fujihara Co. Ltd., Tokyo, Japan) with participants in a supine position. The data were recorded at 1000 Hz and high-pass and low-pass filtered at 0.03 and 200 Hz respectively. The five marker coils were energized before and after each block to determine head movement and position within the MEG dewar. The head movement tolerance was <4 mm in any direction.

MRI data acquisition. High-resolution T1-weighted anatomical magnetic resonance images (MRIs) were acquired in a separate session at Macquarie University Hospital, using a 3T Siemens Magnetom Verio scanner with a 12-channel head coil. Images were obtained using 3D

GR\IR scanning sequence with the following parameters: repetition time, 2000 ms; echo time, 3.94 ms; flip angle, 9°; slice thickness, 0.93 mm; field of view, 240 mm; image dimensions, $512 \times 512 \times 208$.

4. Data analyses

Beamforming analyses. MEG data was epoched from 500 ms before and 900 ms after the onset of the last word and were labelled as the *correct sentence, semantic violation,* and *syntactic violation* (only in experiment two) condition respectively. The MEG data were concatenated across blocks for each condition in each participant and then co-registered with each participant's own structural MRI. All the pre-processing and beamforming analysis were performed using a Matlab toolbox - BrainWave (Jobst et al., 2018, version 3.3; https://cheynelab.ut oronto.ca/brainwave).

To investigate the hippocampal theta power change under different experimental conditions, the synthetic aperture magnetometry (SAM) beamformer (Robinson and Vrba, 1999) was employed to create differential images of source power for 0.5 s of visual stimulation (i.e., 0–0.5 s, 0.1 s–0.6 s, 0.2 s–0.7 s, … 0.4 s–0.9 s respectively, with 0s being the stimulus onset) compared to 0.5 s of baseline (−0.5 s to 0) using a pseudo-T metric (see Isabella et al., 2015 for detailed description of the pseudo-T metric). Previous simulation studies (e.g., Krishnaswamy et al., 2017; S. S. Meyer et al., 2017) and empirical studies (e.g., Pu et al., 2017; Pu, Cornwell et al., 2018; Backus et al., 2016; Cornwell et al., 2012; Cornwell et al., 2008; Pizzo et al., 2019) have shown that MEG measurement in combination with beamforming analysis could reliably detect hippocampal signals (see a review by Pu, Cheyne et al., 2018). A sliding window method was used to achieve balanced covariance estimation between pre and post-stimulus onset periods. Magnetic fields were modelled with a single sphere head model derived from each participant's structural MRI to fit the inner skull surface of each participant's MRI (Lalancette et al., 2011; Sarvas, 1987). A covariance matrix for theta band oscillations (4–8 Hz) was computed from unaveraged 0.5 s of post-stimulus onset window and 0.5 s of pre-stimulus onset baseline window. The total covariance window length for each condition in experiment one was 80 trials $\times$ (0.5 s + 0.5 s) = 80 s, and in experiment two 68 trials $\times$ (0.5 s + 0.5 s) = 68 s. The length of the data covariance windows in the two experiments should be sufficiently enough for a reliable power estimation (Brookes, 2008). The source space was sampled into a three-dimensional grid of 4 mm^3 voxels with an equivalent current dipole source at each location. This analysis produced

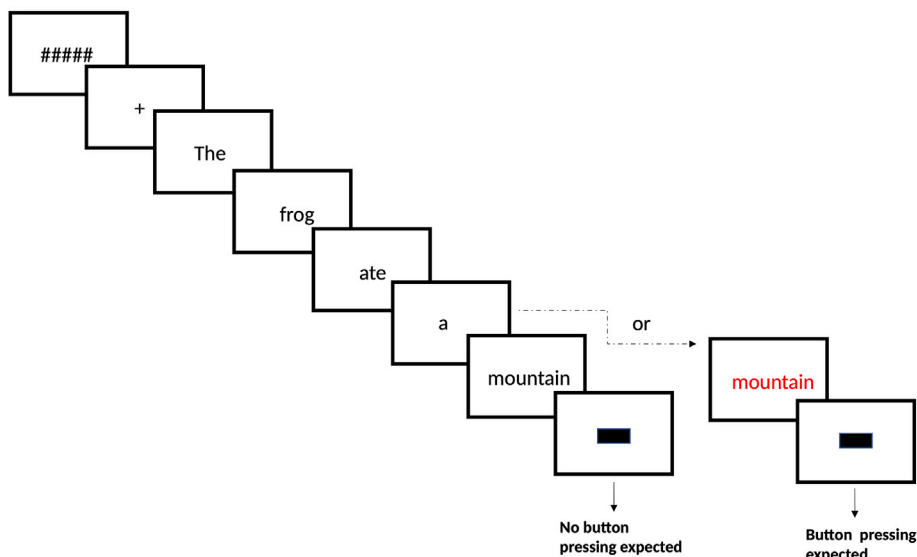## Experimental procedure

Fig. 1. Experimental procedures. Each sentence started with the presentation of '#######' for 500 ms, followed by 500 ms fixation cross ('+'). Each word in a sentence was presented for 500 ms, except for the last word which was presented for 900 ms. Following the presentation of each word, a blank grey screen was presented for 500 ms. At the end of a sentence, a black square was displayed on the screen for 500 ms. The participants were required to press a button if there was a word in red in the sentence after seeing the black square. In study one, the red word always occurred in the position of the last word in a sentence. In study two, the red word occurred in any position in a sentence. The inter-trial-interval (ITI) was randomly selected from a rectangular distribution between 2700 and 3700 ms in experiment one and between 2000 ms and 2500 ms in experiment two.

pseudo-T SAM volumetric images to represent the theta power change (i.e., pseudo-T values) between the active window and baseline window for each condition in each experiment.

Group Statistics. Individual SAM images were normalized to a Talairach brain template in the Analysis of Functional NeuroImages (AFNI) software (https://afni.nimh.nih.gov/). This was achieved by first registering the anatomical images of the individual participants to a Talairach brain template, and obtaining a set of parameters which were then applied to the individual SAM images for normalization. In experiment one, we first examined whether there were significant differences in theta power between time windows for each condition. For this, we compared theta power across all the time windows using the paired t tests with a lenient threshold $p < 0.05$ for each experimental condition. No significant results were seen. Therefore, we averaged theta power over all sliding windows (e.g., Gron et al., 2000; Konishi et al., 2013). We next compared the averaged power in the semantic violation condition to that in the correct sentence condition to determine whether there was a significant difference in hippocampal theta power between the two conditions. The multiple comparison issue was controlled using a small volume FDR correction method within a mask including bilateral hippocampi and parahippocampi, given a strong a priori of the involvement of the hippocampal and parahippocampal structures in violation processing (e.g., Garrido et al., 2015; Kumaran and Maguire, 2007). The threshold was set at $p < 0.005$, $q < 0.05$ throughout the paper if not otherwise specified.

The analytical procedure in experiment two was similar to that in experiment one. Since no differences were found between time windows for each condition, we compared the averaged theta power over all the sliding windows in the hippocampi and parahippocampi between the semantic violation and the correct sentence conditions to replicate the result of experiment one. We then compared the averaged theta power between the syntactic violation and the correct sentence conditions, to examine whether there was also a significant increase in hippocampal and parahippocampal theta power in the syntactic violation condition. Finally, we directly compared the averaged hippocampal and parahippocampal theta power between the semantic and syntactic violation conditions, to further examine whether theta power was significantly stronger in the semantic violation condition.

Time-frequency representations (TFRs). In order to reveal the time-varying change of hippocampal and parahippocampal theta oscillations, TFRs in the peak voxel in the hippocampal and parahippocampal region, which showed a significant theta power increase in the group analyses were constructed for all the conditions separately. First, we reconstructed the source waveform of $-0.5 - 0.9$ s from the voxel we specified. Then, a five-cycle Morlet wavelet frequency transformation was performed on single trial source activity over a frequency range of $3–50$ Hz in 1 Hz steps. Complex wavelets were created using the following formula:

$$w(t, f_0) = A \exp\left(-t^2 / 2\sigma_t^2\right) \exp(2i\pi f_0 t)$$

Wavelets were then normalized so that the total energy was 1, with the normalization factor A being equal to: $(\sigma_t\sqrt{\pi})^{-1/2}$ (Tallon-Baudry et al., 1996). A convolution of the complex wavelet with the MEG source waveform was then derived, and the magnitude of this convolution was used to create each TFR. The value was then converted to percentage change in power relative to the pre-trial baseline ($-0.5 - 0$ s).

Connectivity analysis. To determine whether and how the hippocampal formation coordinates with neocortical language areas (Covington and Duff, 2016), we investigated the functional connectivity between the hippocampus and parahippocampus and the language areas showing a significant effect in the whole brain analyses. To this end, we first examined the pattern of theta power change across the whole brain, to find out what areas other than the hippocampus and parahippocampus showed a significant theta power increase in the semantic violation vs. the correct sentence condition ($p < 0.005$, $q < 0.05$, FDR corrected across

the whole brain). We pooled the data together from experiment one and two for the semantic violation condition and the correct sentence condition respectively, since the fundamental objectives of the two conditions were the same across the two experiments. We then quantified the hippocampal-neocortical interaction during online sentence reading by computing phase-locking value (PLV) using the theta phase time series in the peak voxels from the significant hippocampal and parahippocampal regions and the significant neocortical language areas. The PLV was computed separately for experiment one and two, in order to examine whether the pattern of the PLV was consistent across experiments (i.e., replicability).

The PLV is a metric that can be used to investigate task-induced changes in long-range synchronization of neural activity (Lachaux et al., 1999). To calculate the PLV, we first obtained the mean-subtracted theta (4–8 Hz) time course from 0 to 0.8s (0 was the word onset. The last 0.1s was trimmed due to a possible edge effect) in the specified voxel generated using SAM beamforming algorithm described above, for each trial type in experiment one and two separately. The Hilbert transform was then performed on the mean-subtracted single trial data, and the instantaneous phase was obtained from the angle of the complex Hilbert transform. Using Equation 1 shown below, the PLV was computed as the resultant vector length of phase differences between two signals over trials, such that a larger value indicates less variability in the phase difference across trials.

4.1. Equation 1: The phase locking value (PLV)

$$PLV(t) = \frac{1}{N} \left| \sum_{n=1}^{N} e^{i\theta(t,n)} \right|$$

where N is the number of trials and $\theta(t, n)$ is the difference between the instantaneous phase of the two signals at time t and trial n. We computed the PLV across trials instead of the PLV across time, because the connectivity between two brain areas might be transient (e.g., Baker et al., 2014). Moreover, the PLV across trials provides stronger evidence for task-related modulations in connectivity relative to the PLV across time, because the connectivity must be in the same phase configuration on each trial (Cohen, 2014, p.340).

In our analyses, we first computed the PLV in the semantic violation condition of the time period of 0–0.8s, since there was an increase in theta power in this condition compared to the other experimental conditions. To determine the statistical significance of the observed PLV, a permutation test was performed. Specifically, we temporally shifted the phase time series of one signal by a random temporal offset without changing the phase angle time series of the other. The PLV was then recomputed using Equation 1. This procedure was repeated 1000 times, generating a distribution of the maximum PLVs expected under the null hypothesis. The significance threshold was set at the 95th percentile of the distribution of the maximum PLVs.

To further explore whether the significant PLV was specific to the semantic violation condition or general across all condition types during sentence reading, we first examined whether there was significant PLV in the correct sentence condition and the syntactic violation condition as well. We computed the PLV and the statistical threshold in the two conditions separately using the procedure described above. To further examine whether there was a significant difference between conditions, we compared the PLV in the correct sentence condition and the syntactic violation condition separately to that in the semantic violation condition using the paired *t*-test for every time point separately. The original statistical threshold was set at $p = 0.05$. If there were time points whose p values were found <0.05, FDR method was applied for correcting multiple comparisons.

One concern that arises from conducting connectivity analysis using M/EEG data is volume conduction or signal leakage. Signal leakage

causes the phase lag between two signals to be either 0 or π (referred to as zero lag), which causes false positive PLV results. To test for the possible contamination of signal leakage in our dataset, the V-test (Zar, 1999), a commonly used procedure of testing for volume conduction (see Cohen, 2014, pp. 352–355 for more information) was conducted using a Matlab Circular Statistic toolbox (Berens, 2009). Briefly, in the V-test, a vector of phase angles was tested against a specified angle (e.g., 0 or π) under the null hypothesis that the vector of angles is not clustering around the angle specified. If there is no strong volume condition, a non-significant p value (>0.05) was expected (that is, the null hypothesis that the phase angle is not 0 or π cannot be rejected). In our analyses, we first extracted the mean phase angle difference averaged across all the trials and time points for each participant in both experiments, which resulted in one value for each participant. Then we tested the vector of the phase angle differences of all the participants against 0 and π. If a non-significant p value was obtained, we should have stronger confidence against the possible contamination of signal leakage in our dataset. To visually confirm this, we plotted the circular histogram of the phase angle differences of all the participants in the two experiments. In case of strong signal leakage, a clustering around 0 or π should be observed in the histogram.

To further confirm that the connectivity pattern observed based on the PLV metric was robust and not due to signal leakage, we quantified phase coupling between the hippocampal formation and the left STG using another metric, i.e., the weighted phase-lag index (wPLI, Vinck et al., 2011) (see Equation 2 below), which is sensitive to zero-lag.

4.2. Equation 2: The weighted phase-lag index (wPLI)

$$wPLI(t) = \frac{\left| N^{-1} \sum_{n=1}^{N} |imag(Sxy(n,t))| sgn(imag(Sxy(n,t))) \right|}{N^{-1} \sum_{n=1}^{N} |imag(Sxy(n,t))|}$$

in which N is the number of trials; $imag(S_{xy(n,t)})$ indicates the imaginary part of the cross-spectral density of signal X and Y on the nth trial at time point t; sgn indicates the sign (−1 for negative values, +1 for positive values, and 0 for zero values).

The wPLI is an extension of the phase-lag index in which the sign of phase angle differences are weighted according to the magnitude of the imaginary component of the cross-spectrum. It is sensitive to zero-lag between signals, and compared to the phase-lag index, it reduces sensitivity to additional, uncorrelated noise sources and increased statistical power to detect changes in phase-synchronization. To determine the statistical threshold, we used a permutation procedure by shifting one signal by a random temporal offset while keeping the other one unchanged, similar to what was employed in the PLV analyses.

Exploratory analyses. Given the possibility that the frequency of theta oscillations might be lower than 4–8 Hz (Jacobs, 2014), we conducted a similar beamforming analysis as described above for 1–4 Hz, to explore whether a significant effect could also be observed for the lower frequency oscillations in the hippocampal formation.

5. Results

In both experiments, the accuracy of button pressing for detecting a red word during sentence reading was high (mean = 93.97%, s.d. = 10.75%), indicating close attention of the participants.

5.1. Hippocampal and parahippocampal theta power during sentence reading

Experiment one. We found significantly increased theta power in the right hippocampus and parahippocampus in the semantic violation compared to the correct sentence condition (peak voxel in the right parahippocampus, Talairach coordinate: x = 26, y = −17, z = −16, t score = 6.84, Fig. 2A and B). Time frequency representations (TFRs)

confirmed that there was no pronounced increase in theta power in the correct sentence condition relative to a pre-trial baseline in the hippocampal formation, while there was a pronounced increase in theta power in the semantic violation condition (Fig. 2C) .

Experiment two. We replicated the finding from experiment one: i.e., compared to the correct sentence condition, there was significantly enhanced theta power in the semantic violation condition in the right hippocampus and parahippocampus (peak voxel in the right hippocampus, Talairach coordinate: x = 34, y = −9, z = −12, t score = 3.37, Fig. 3A and B). No significant increase in theta power in the syntactic violation condition was found in the bilateral hippocampi and parahippocampi. Directly comparing the semantic to syntactic violation condition revealed significantly stronger theta power in the right hippocampus and parahippocampus in the semantic violation condition (peak voxel in the right hippocampus, Talairach coordinate: x = 30, y = −13, z = −8, t score = 3.91, Fig. 3 C & B). TFRs (Fig. 4) confirmed that only in the semantic violation condition, there was a pronounced increase in theta power relative to a pre-trial baseline.

Previous iEEG studies (e.g., McCarthy et al., 1995) using a similar semantic violation paradigm have reported a late negative potential (the timing of the peak fell into the range of approximately 0.6–0.8s) in the hippocampal formation in the semantic violation vs. the correct sentence condition. To find out whether in our dataset, a similar late negative potential could also be observed, we source-reconstructed the activities of 0.03–48 Hz from the peak voxel of the hippocampal formation, separately for the semantic violation and the correct sentence conditions. Collapsing the data over the two experiments, we found a clear late negative potential (Supplementary Fig. 1, p = 0.04, t = −2.136 for the averaged time window of 0.67–0.77s). However, such a pattern of results was not observed in the syntactic violation vs. the correct sentence condition (Supplementary Fig. 2).

5.2. Hippocampal-neocortical interaction during sentence reading

Since the fundamental objectives for the semantic violation and the correct sentence conditions were the same in experiment one and two, we pooled the data from the two experiments together for the two conditions respectively to examine the theta power change across the whole brain. We found that compared to the correct sentence condition, besides in the right hippocampus and parahippocampus (Talairach coordinate of the peak voxel peak voxel: x = 34, y = −9, z = −20, t score = 5.93), significantly increased theta power was also observed in the left inferior prefrontal region (Talairach coordinate of the peak voxel peak voxel: x = −22, y = 31, z = −4, t score = 7.81), left superior temporal gyrus (Talairach coordinate of the peak voxel peak voxel: x = −42, y = −34, z = 16, t score = 6.28), left fusiform gyrus (Talairach coordinate of the peak voxel: x = −42, y = −37, z = −12, t score = 5.52), right middle frontal gyrus (Talairach coordinate of the peak voxel: x = 18 y = −5, z = 56, t score = 6.64), and right cerebellum (Talairach coordinate of the peak voxel: x = 18, y = −65, z = −52, t score = 5.62), left middle occipital gyrus (Talairach coordinate of the peak voxel: x = −50, y = −65, z = −4, t score = 6.13) (Fig. 5A).

We also compared theta power in the syntactic violation to the correct sentence condition in the second experiment across the whole brain. Significantly increased theta power was found in the left frontal gyrus (Talairach coordinate of the peak voxel: x = −24, y = 49, z = 20, t score = 5.06), right frontal and cingulate gyrus (Talairach coordinate of the peak voxel: x = 18, y = 31, z = 4, t score = 5.16), left declive (Talairach coordinate of the peak voxel: x = −6, y = 3, z = 40, t score = 6.16), left insula (Talairach coordinate of the peak voxel: x = −46, y = −5, z = 12, t score = 4.77), and left middle frontal gyrus (Talairach coordinate of the peak voxel: x = −26, y = 3, z = 44, t score = 5.02) (Supplementary Fig. 3). These brain areas generally agreed with previous reports (e.g., Kaan and Swaab, 2002).

The left inferior frontal gyrus (IFG) and left superior temporal gyrus (STG) are two key brain areas for language processing commonly
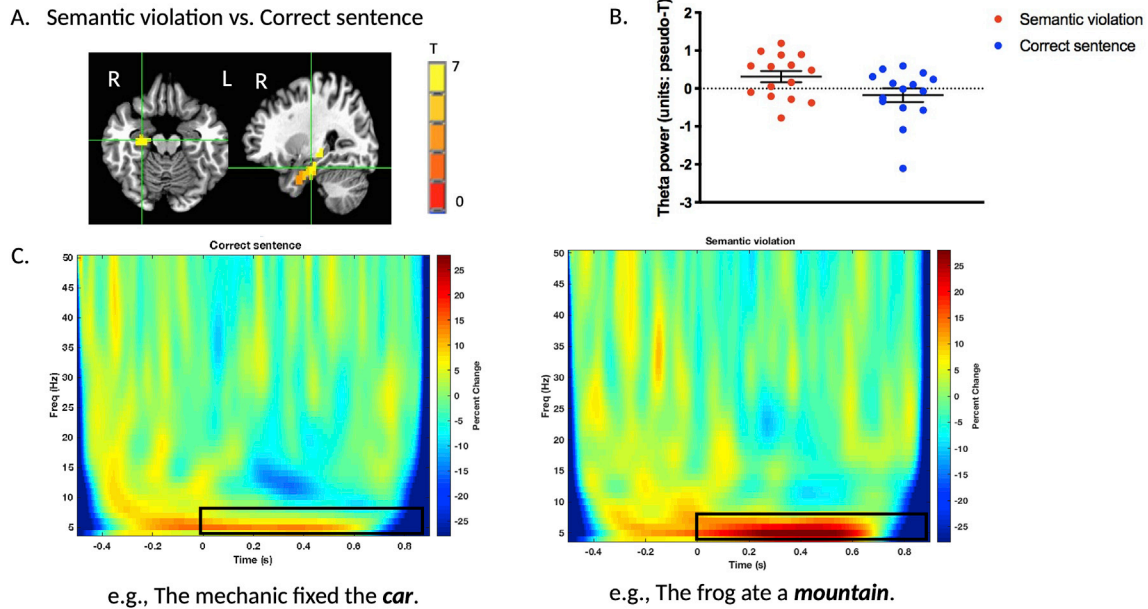
Experiment 1

Fig. 2. Theta power change in the hippocampus and parahippocampus during reading the last word of a sentence in experiment one. A. Significantly increased theta power in the hippocampus and parahippocampus averaged over all the sliding windows in the beamforming analyses in the semantic violation vs. the correct sentence condition with the peak voxel in the right parahippocampus (Talairach coordinate: x = 26, y = −17, z = −16, p < 0.005). B. Cluster mean of theta power (units: Pseudo-T) in the significant hippocampal and parahippocampal region shown in Fig. 2A in the semantic violation condition and the correct sentence condition respectively. C. Time frequency representations (TFRs) in the peak voxel in Fig. 2A in the semantic violation condition and the correct sentence condition. Black square indicates the duration from the onset of the last word.
Error bar denotes ± 1 standard error of the mean.

reported in previous work using similar language tasks (e.g., Friederici et al., 2003; Hagoort et al., 2004). In order to quantify the functional connectivity between the hippocampus and those canonical language areas, we computed the theta phase locking value (PLV) between the right hippocampus and parahippocampus and the left IFG and the left STG respectively in the semantic violation condition separately for
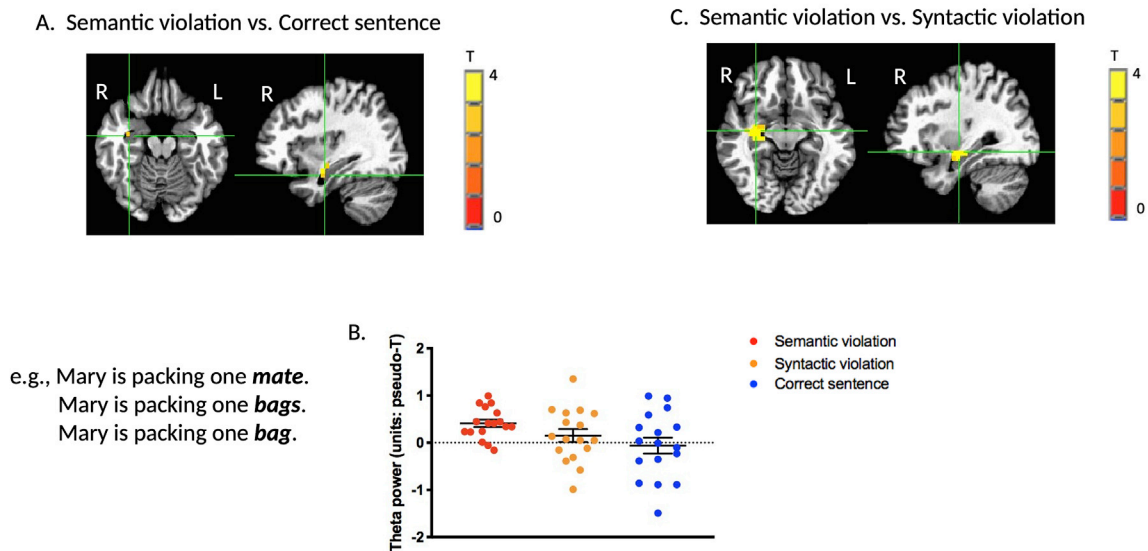
Experiment 2

Fig. 3. Theta power change averaged over all the sliding windows in the beamforming analyses in the hippocampus and parahippocampus during reading the last word of a sentence in experiment two. A. Significantly increased theta power in the hippocampus and parahippocampus in the semantic violation vs. the correct sentence condition, with the peak voxel in the right hippocampus (Talairach coordinate: x = 34, y = −9, z = −12, p < 0.005). B. Significantly increased theta power in the hippocampus and parahippocampus in the semantic vs. syntactic violation condition, with the peak voxel in the right hippocampus (Talairach coordinate: x = 30, y = −13, z = −8, p < 0.005). C. Cluster mean of theta power increase (units: Pseudo-T) in the significant hippocampal and parahippocampal region shown in Fig. 3A and B in the correct sentence condition, the semantic violation condition and the syntactic violation condition respectively.
Error bar denotes ± 1 standard error of the mean.

experiment one and two. We found that the right hippocampus and parahippocampus exhibited significantly enhanced transient phase synchronization with the left STG, with the time course of theta phase synchrony being similar in both studies (Fig. 5B).

To examine whether the significant connectivity was specific to the semantic violation condition, we computed the PLV over trials for the correct sentence condition and the syntactic violation condition respectively. Both conditions showed significantly transient phase coupling between the hippocampus and left STG (supplementary Fig. 4). To examine whether there were significant differences between conditions, we compared the PLV in each of the two conditions to the PLV in the semantic violation condition using the paired *t*-test across time points. No significant difference was found in those comparisons (supplementary Fig. 5), indicating the cross-regional communication between the hippocampus and the left STG might be general across sentence types.

No significant p value (p = 0.11 and 0.88 for the testing against 0 and π respectively) was obtained from the V-test (see methods session for details), suggesting the phase angle difference between the hippocampus and the left STG across participants was neither 0 nor π, which significantly increased our confidence against the possible influence of signal leakage on the PLV results shown in Fig. 5B. For visual confirmation, we plotted the circular histogram of the phase angle differences of all the participants from both experiments averaged over trials and all the post-stimulus onset time points (Fig. 5C, left panel), similar to what has been shown in Backus et al. (2016) (Supplementary Fig. 4 in their paper). No obvious clustering around 0 or π was seen in the histogram. For visualization purposes, in Fig. 5C (right panel), we also plotted the circular histogram of the phase angle differences of all the participants averaged over trials and the significant time points (i.e., those time points whose PLV exceeded the significance cutoff in Fig. 5B).

No significant PLV was found between the hippocampus and parahippocampus and the left IFG in both studies. For exploratory purposes, we computed the PLV between the left IFG and left STG. No significant results were observed either, indicating the specificity of the significant

phase coupling between the hippocampus and the left STG during online sentence reading.

Finally, to further confirm the significant phase coupling shown in Fig. 5B was robust and not due to signal leakage, we used the weighted phase-lag index (wPLI), a metric which is sensitive to zero-lag to quantify phase coupling. We found significantly transient wPLIs between the hippocampus and left STG (supplementary Fig. 6), arguing further that the significant phase coupling shown in Fig. 5B should not be due to signal leakage.

For a lower frequency range of 1–4 Hz, no significant effects were observed in the bilateral hippocampi and parahippocampi as for 4–8 Hz.

6. Discussion

Using non-invasive MEG measurement and the violation paradigm, which was commonly used in previous language studies (e.g., Hagoort et al., 2004), our present study investigated whether and how hippocampal theta supports online language processing, and whether and how theta coordinates the communication between hippocampus and canonical language areas. The main findings are as follows: 1) There was a significantly increase in theta power in the hippocampus and parahippocampus in the semantic violation vs. the correct sentence condition, and the pattern of findings was replicated using different sentence stimuli in a different cohort of participants; 2) No noticeable theta power increase in the hippocampus and parahippocampus was found in the syntactic violation vs. the correct sentence condition; 3) Significantly enhanced transient theta phase coupling was found between the hippocampus and the left superior temporal gyrus (STG), a hub area of the cortical network for language comprehension and semantic processing (Binder, 2015; Binder et al., 2009; Hickok and Poeppel, 2000).

The finding that more theta power was observed in the semantic violation relative to the correct sentence condition is in line with the findings of Hagoort et al. (2004), where they found enhanced theta power in processing semantic incorrect vs. correct sentences. That the
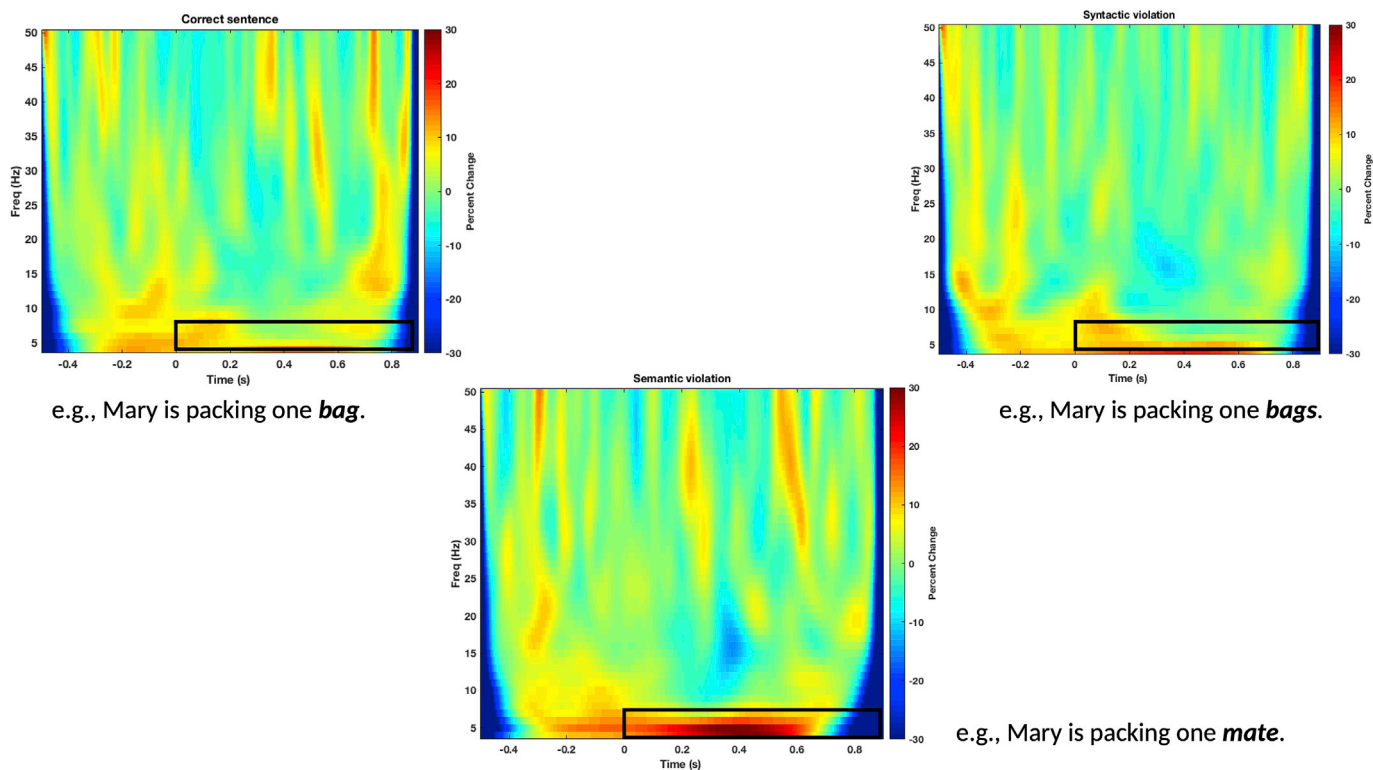

Fig. 4. Time frequency representations (TFRs) in the peak voxel shown in Fig. 3A in different experimental conditions in experiment two. Black square indicates the duration from the onset of the last word.
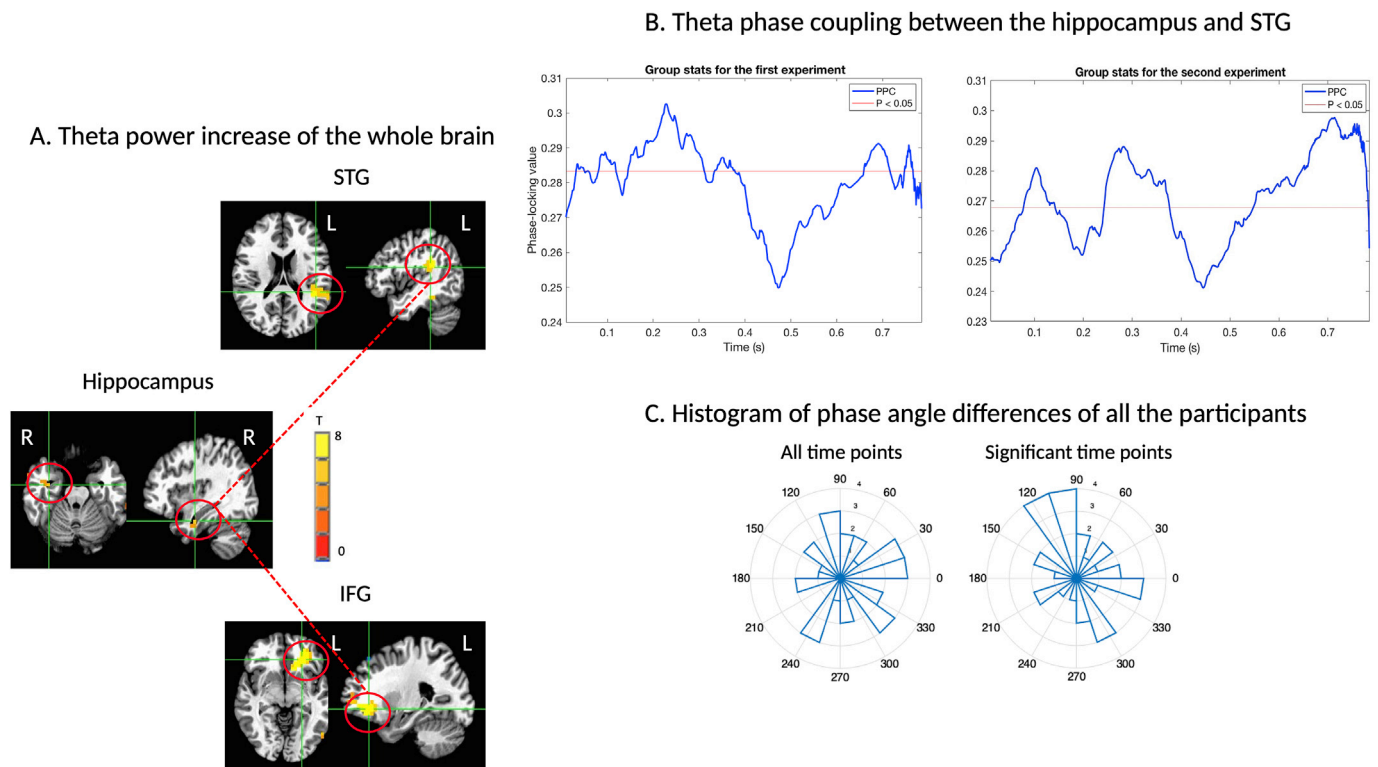
B. Theta phase coupling between the hippocampus and STG

A. Theta power increase of the whole brain

C. Histogram of phase angle differences of all the participants

Fig. 5. Theta phase synchrony between the hippocampus and neocortical regions in the semantic violation condition during reading the last word of the sentence. A. Whole brain patterns of significant theta power increase in the semantic violation vs. the correct sentence condition, collapsed over the two experiments (N = 32, p < 0.001, FDR corrected acorss the whole brain) and averaged over all the sliding windows in the beamforming analyses. Six slices of the whole brain images were shown in order to highlight the following three areas used for the connectivity analyses: the right hippocampus and parahippocampus (Talairach coordinate of the peak voxel peak voxel: x = 34, y = −9, z = −20), left superior temporal gyrus (STG) (Talairach coordinate of the peak voxel peak voxel: x = −42, y = −34, z = 16) and left inferior frontal gyrus (IFG) (Talairach coordinate of the peak voxel peak voxel: x = −22, y = 31, z = −4). B. Theta phase coupling computed using the phase locking value (PLV) across trials between the right hippocampus and left STG from the onset of the last word (0s) to 0.8s in experiment one and two. The last 0.1s was cut to avoid the possible edge effect. Significantly enhanced transient phase coupling was found in both experiments. The red line denotes the p = 0.05 cutoff obtained from the permutation procedure (see methods section for details). C. Circular histogram of theta phase differences between the right hippocampus and left STG of all the participants averaged over trials and all the time points (left panel in Fig. 5C) or averaged over all the trials and the significant time points (i.e., those time points whose PLV exceeded the significance cutoff shown in Fig. 5B) (right panel in Fig. 5C). No cluttering around zero or pi is observed in both histograms by visual inspection, in line with the results from V-test (see the results section), thus arguing against the possibility of the contamination of volume conduction in our dataset. Visual inspection confirms that there is a more obvious bias in the distribution of the phase angle differences averaged over the significant time points vs. all the time points (including both significant and non-significant time points), which is consistent with the statistical results obtained from the permutation procedure shown in Fig. 5B. These results also indicate that computing PLVs over trials instead of time is better at revealing transient phase synchrony, which might not be seen when all the time points are averaged together.

increased theta power was localized to the hippocampus and parahippocampus serves as direct evidence for the speculation put forward by Hagoort et al. (2004), i.e., the increased oscillatory theta power observed at the scalp level involves contribution from the hippocampus. Furthermore, we did not find significant hippocampal theta power increase when participants read a syntactically incorrect ending compared to a correct sentence ending. This pattern of results may suggest that hippocampal and parahippocampal theta oscillations do not respond to any type of linguistic information. This idea has been confirmed by the result that there was significantly stronger hippocampal and parahippocampal theta power in processing semantic vs. syntactic violation. Our findings generally agree with findings from fMRI studies that hippocampal activation increases in lexical-semantic vs. syntactic prediction (Bonhage et al., 2015), and that the hippocampus is related to semantic composition but not to syntactic composition (Blank et al., 2016). Therefore, all the findings seem to point to a direction that hippocampal theta oscillations are specifically linked to semantic-related processing. This idea is corroborated by previous hippocampal lesion studies. For instance, bilateral medial temporal lobe damage in patient HM did not affect his grammatical processing (Kensinger et al., 2001), while patients with hippocampal amnesia performed significantly worse on word meaning-related measures, such as productive and receptive measures of

vocabulary depth and semantic richness (Klooster, 2016, see Duff and Brown-Schmidt, 2012 for a review).

Taking together the findings of our present study and Piai et al. (2016), we speculate that the shared mechanism of language and memory might be associated with a critical role of the hippocampus in semantic memory (e.g., Duff et al., 2020; Manns et al., 2003) and the capacity of the hippocampus for predicting and simulating the future events based on past experience (Eichenbaum and Fortin, 2009; Schacter et al., 2012). In Piai et al. (2016), constraint contexts facilitate lexical and semantic prediction of the upcoming words based on stored knowledge. In our present study, semantic incongruent words violate the lexical-semantic prediction formed as a sentence unfolds based on sentence context and existing knowledge. Therefore, during sentence reading, the role of hippocampal theta may be associated with semantic retrieval and prediction based on previous knowledge.

One may argue that the violation paradigm used in the present study may also tap into integration process, i.e., semantic violation of the last word increases the difficulty of the integration of the meaning of the upcoming words into the meaning built up during reading (Kutas et al., 2011; Kutas and Federmeier, 2011). Integration process is thought to reflect bottom-up processing, while prediction process top-down processing. Similar to prediction process, integration process can also be

supported by the hippocampus through its capacity for relational binding. In our view, prediction and integration processes might not be mutually exclusive to each other, and both prediction errors and integration difficulties need to draw on previous knowledge. Moreover, to make possible the rapid comprehension of language in our brain, the bottom-up and top-down processing might be in parallel. Future studies using clever experimental manipulations, which allow a clear differentiation of the two processes (e.g., Mantegna et al., 2019) can help clarify the exact role of hippocampal theta in meaning-related processing.

Previous studies have also demonstrated that hippocampal theta also respond to other types of stimuli in a similar violation paradigm, such as faces (Gruber et al., 2018) and objects (Axmacher et al., 2010; Garrido et al., 2015). Therefore, these findings together with our present findings may suggest a modality-free processing of concepts in the hippocampal formation, which echoes with the growing consensus that the hippocampal formation supports the creation and retrieval of a domain-general cognitive map of concepts via a fundamental theta-based mechanism (Solomon et al., 2019; Spiers, 2020). However, semantics/concpets are generally thought to be stored in distributed networks in the neocortex (Binder et al., 2009). A natural question is raised: does the hippocampal formation store any sort of semantic/conceptual information or just relations between concepts? Previous studies seem to suggest that both types of information may be decoded from the hippocampal formation. Solomon et al. (2019) have shown that the magnitude of hippocampal theta power is associated with the semantic distance between words. Reber et al. (2019) have reported that semantic category can be decoded from the activity of populations of human single neurons in the hippocampus and other areas in the medial temporal lobe. Future studies could consider examining whether semantic category can also be uncovered through population electrical/magnetic signals recorded by iEEG and MEG, especially through theta oscillations. This may open up new lines of research without measuring single neurons. Emerging evidence from recent studies support the notion that information carried out by single neurons can be revealed by signals measured by iEEG/MEG. For instance, some studies (e.g., Chen et al., 2018; Maidenbaum et al., 2018; Staudigl et al., 2018) have demonstrated that similar to single grid cells, theta and gamma activities, measured in the entorhinal cortex with iEEG or MEG, are hexadirectionally modulated according to either movement direction during virtual navigation or the direction of eye movement.

Importantly, our present study has demonstrated that hippocampal signals could be robustly measured using non-invasive MEG recordings, similarly to what has been measured with iEEG using a similar experimental paradigm (e.g., McCarthy et al., 1995). Many E/MEG studies have used either dipole fitting or distributed source localization algorithms (e.g., minimum norm estimation) to localize the ERP/Fs (e.g., Lau et al., 2013). Most of the studies have not reported the hippocampus as one of the sources. Using dynamic causal modelling, David et al. (2011) compared models including vs. excluding the hippocampus in language processing and showed that the model including the hippocampus outperforms those excluding the hippocampus, which implies that the hippocampus might be important for language processing. In the present study, using a beamforming source localization technique, we directly localized the hippocampal activities with MEG data. The results are robust, as we replicated the patterns of findings in an independent study with a different set of experimental stimuli and in a different cohort of participants. Therefore, theses findings demonstrate that whole-head MEG recordings in combination with beamforming source localization techniques (S. S. Meyer et al., 2017) provide an avenue to study human hippocampal rhythms without completely depending on the rare opportunities of recordings from the brain of the pre-surgical patients.

There is an ongoing debate as to whether the hippocampus is only involved in the initial acquisition of new information, or persistently engaged in the later stage of processing, although the information has been thought to become hippocampus-independent after the newly encoded memory traces have been transformed into long-term memory (i.e., memory consolidation). Our current results may help reconcile the

debate by showing that the involvement of the hippocampus after consolidation depends on the information type being processed. If semantic meaning is processed, the hippocampus may be actively engaged at all stages. If rules (e.g., grammar) are processed, the hippocampus may only involve in the initially encoding; after consolidation, the neocortex may be in charge of the processing. In line with this idea, Friederici et al. (2006) have reported that increased exposure to new grammatical rules leads to decreased activities in the hippocampus and increased activities in the neocortex. In contrast, P. Meyer et al. (2005) observed enhanced hippocampal response during syntactic processing. However, it should be noted that the syntactic violation sentences in P. Meyer et al. (2005)'s study were created by adding an ungrammatical preposition *on* to the grammatical sentence, e.g., "the shop was being *on* closed", which may also lead to a different lexical semantic prediction, e.g., "the shop was being on [fire]". Therefore, the hippocampal response observed in P. Meyer et al. (2005) in the syntactic violation condition might just reflect semantic-related processing.

Future research using learning paradigms could be conducted to systematically investigate how the hippocampus contributes to initial learning and later processing after memory consolidation for semantic and syntactic processing respectively. Furthermore, to more tightly link the hippocampal theta activities to the behaviour performance, future studies could consider parameterization of the level of semantic violation, such as letting participants rate the degree of surprise during sentence reading, similarly to what has been done in some of the early language studies (e.g., Opitz and Friederici, 2003). A positive correlation between the hippocampal theta power and the level of semantic violation is expected. Moreover, in our present study, we only investigated word meaning (referred to as semantic domain) and morphosyntactic processing (referred to as syntactic domain). Future studies could explore whether a similar pattern of results could be generalized to world meaning processing (referred to as pragmatic domain) and other types of syntactic processing (e.g., word category).

It is notable that the effects of theta oscillations in the present experiments exhibit different patterns of hemispheric lateralisation in the neocortex and the hippocampus, with the neocortical theta showing a left hemispheric bias and the hippocampal theta a right hemispheric bias. Left–right asymmetry is a key feature of the structure and function of the human brain (Kong et al., 2018: Kong, Boedhoe et al., 2019; see Kong, Postema et al., 2019 for a review). The left hemisphere dominance of the neocortex for language processing has been supported by many previous language research (e.g., Frost et al., 1999; Kong, Tzourio-Mazoyer et al., 2019), while there is less consideration for hemispheric differences in the hippocampus (Jordan, 2019). However, emerging evidence from studies on navigation and memory seems to suggest that the left and right hippocampus play different roles (e.g., Pu et al., 2017; Miller et al., 2018; Kong et al., 2017). For instance, in navigation, the right hippocampus appears to be crucial for the holistic environmental learning, while the left hippocampus crucial for the binding of an object to a specific location (Pu et al., 2017). In the present study, we only observed right hippocampal theta responding to semantic violation. This pattern of lateralisation is unexpected, since language processing is generally thought to be more biased to the left hemisphere (Friederici, 2011). In contrast, in Piai et al. (2016), theta power increase has been observed in bilateral hippocampi. A number of possibilities can be attributed to the discrepancy. First, the tasks used in the two studies are different, which may tap into both overlapping and differential aspects of sentence processing. Piai et al. (2016)'s study modulated contextual constraint of a sentence, while our study modulated semantic congruency. Hippocampal theta might respond differentially to the two aspects of semantic processing. The right hippocampal theta activity observed in our present study might be linked to an idea that the right hippocampus contributes preferentially to memory benefits of the concreteness of words (Kounios and Holcomb, 1994; Paivio, 1986), one important feature of the semantic task used in our study. Second, our study recorded brain signals of healthy participants, while Piai et al. (2016) directly recorded from the brains of

epilepsy patients, with the epileptic zone being in the medial temporal lobe. Future (non-invasive) studies could consider conducting the same experiment as used in Piai et al. (2016) on healthy participants to further examine the possible functional differentiation of the hippocampi. In addition, since in natural language, ungrammatical or nonsensical words and sentences (key modulations in the violation paradigm) are extremely rare (Baayen, 2014), future studies could also consider using a more naturalistic paradigm (such as naturally read naturalistic stimuli) in combination with eye tracking and iEEG or MEG recordings.

Our third finding is that there was significantly enhanced transient theta phase coupling between the hippocampus and the superior temporal gyrus (STG), in line with the idea that theta oscillations play an important role in inter-regional coordination (Benchenane et al., 2010). However, this significant phase coupling was found not to be specific to the semantic violation condition, and instead general across all the experimental conditions during sentence reading. STG is an important area for language comprehension and is thought to be one of the important language areas for storing semantic information (Binder, 2015; Binder et al., 2009; Hickok and Poeppel, 2000). The hippocampus is an important area for memory. Therefore, the transient coupling between the hippocampus and the left STG during sentence reading may provide an important channel that links the memory and language systems for communicating and binding information from different sources, a process necessary to the generation of sentence meaning. As a sentence unfolds over time, our brain predicts the upcoming words based on the context and existing knowledge, and then encodes the incoming word, retrieves its meaning, and integrates the word meaning into the overall representation gradually established during reading to make sense of the sentence; upon completion, the meaning of the sentence may be further incorporated into our existing knowledge base to keep a record of the sentence – as a result we feel familiar the second time we encounter the same sentence. The theta phase-based coupling did not exhibit differences between semantic violation vs. other experimental conditions, which seems to suggest that the significant theta phase coupling is a fundamental mechanism that supports sentence comprehension, as all sentence types involve similar neural processes necessary to the generation of sentence meaning. Future studies could consider examining the specific computations the functional connectivity may implement, which will help us fully understand what information the phase coupling may convey and why there was no increased connectivity in the semantic violation condition vs. other conditions.

In summary, we observed hippocampal theta oscillations during on-line language processing using non-invasive MEG recordings. No noticeable hippocampal theta was observed in the non-semantic violation conditions (e.g., the syntactic violation condition), suggesting that hippocampal theta is specifically responsible for semantic/meaning-related processing in language. There was significant theta phase coupling between the hippocampus and the left STG. This significant phase coupling may serve as a fundamental mechanism that links the memory and language systems for the generation of sentence meaning. Taken together, our present findings help clarify the functional role of hippocampal theta in language, and contribute to a better understanding of how two important but previously independently studied human abilities – language and memory interface. Therefore, our findings may provide novel and critical insights for the theoretical and computational modelling of both memory and language processing. Finally, our present studies demonstrate that MEG deep source imaging provides an avenue to study the human hippocampal (dys)functioning non-invasively in routine experimentations (Pu, Cheyne et al., 2018).

Declaration of competing interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Yi Pu: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Douglas Cheyne:** Software, Methodology, Writing - review & editing. **Yanan Sun:** Investigation, Writing - review & editing. **Blake W. Johnson:** Conceptualization, Project administration, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116782.

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