A new insight into sentence comprehension
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Published in:
Neuropsychologia

DOI:

Publication date:
2018

License:
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Document Version:
Accepted author manuscript

Link to publication

Citation for published version (APA):

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PII: S0028-3932(17)30467-0
Reference: NSY6593

To appear in: Neuropsychologia

Received date: 16 February 2017
Revised date: 20 November 2017
Accepted date: 1 December 2017


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A New Insight into Sentence Comprehension: the Impact of Word Associations in Sentence Processing as Shown by Invasive EEG Recording.

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Abstract

The effect of word association on sentence processing is still a matter of debate. Some studies observe no effect while others found a dependency on sentence congruity or an independent effect. In an attempt to separate the effects of sentence congruity and word association in the spatio-temporal domain, we jointly recorded scalp- and invasive-EEG (iEEG). The latter provides highly localized spatial (unlike scalp-EEG) and high temporal (unlike fMRI) resolutions. We recorded scalp- and iEEG in three patients with refractory epilepsy. The stimuli consisted of 280 sentences with crossed factors of sentence congruity and within sentence word-association. We mapped semantic retrieval processes involved in sentence comprehension onto the left temporal cortex and both hippocampi, and showed for the first time that certain localized regions participate in the processing of word-association in sentence context. Furthermore, simultaneous recording of scalp- and iEEG gave us a direct overview of signal change due to its propagation across the head tissues.

Keywords: invasive EEG; sentence processing; word association; N400; P600

1. INTRODUCTION

Language comprehension is highly incremental in that meaning is assigned to linguistic signal on a word-by-word basis (Tanenhaus et al., 1995). Hence, understanding language processing entails understanding how an incoming word is processed in light of the words preceding it. The measurement of event-related brain potentials (ERPs)—scalp-recorded voltage fluctuations caused by post-synaptic potentials—has been important in furthering our understanding of such incremental comprehension, as ERPs provide a multi-dimensional window into the nature and time-course of cognitive processing. That is, each word of a sentence triggers a profile of systematic voltage deflections in the ERP signal, called components, each of which is taken to index the neural activity underlying a specific computational operation carried out in a given neuroanatomical module (Näätänen and Picton, 1987).

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To language processing, two ERP components are of particular salience: the N400 component and the P600 component (see Kutas et al., 2012, for a review). It has been well established that every incoming word modulates the amplitude of the N400 component (Kutas, 1993), a negative deflection in the ERP signal that reaches maximum 400ms post word-onset. In general, word-induced N400 amplitude is a measure of the semantic fit between the current word and the word(s) preceding it, with a better fit leading to smaller amplitude (see Kutas and Federmeier, 2011, for an overview). The P600 component, in turn, is a positive deflection in the ERP signal that is maximal about 600ms post word-onset, and is sensitive to a wide spectrum of word-induced interpretational problems, ranging from problems of a syntactic nature (for an overview, see Gouvea et al., 2010), to problems of a semantic (Bornkessel-Schlesewsky and Schlesewsky, 2008; Brouwer et al., 2012; Kuperberg, 2007) or pragmatic nature (Hoeks and Brouwer, 2014). As for the functional interpretation of these components, empirical evidence and theorizing seem to converge on the view that the N400 component indexes the (non-compositional) retrieval of word meaning from memory (e.g., Brouwer et al., 2012; Kutas and Federmeier, 2000; E F Lau et al., 2008; van Berkum, 2009), whereas more recently the P600 has been suggested to index (compositional) processes of mental model updating (Brouwer et al., 2012). These ideas are combined in the Retrieval-Integration (RI) model of the electrophysiology of language comprehension (Brouwer et al., 2012; Brouwer and Hoeks, 2013), which has recently received support from explicit (neuro)computational modeling (Brouwer et al., 2017). On the RI account, every word modulates N400 amplitude, indexing the retrieval of its associated meaning from semantic memory. Retrieval of word meaning is facilitated if the conceptual knowledge associated with an incoming word is already (partially) pre-activated in semantic memory due to contextual and/or lexical priming, leading to a reduction in N400 amplitude. Every word also modulates P600 amplitude, reflecting the integration of its retrieved meaning with the unfolding utterance representation, to produce an updated utterance representation. These integrative processes may intensify when the unfolding utterance representation requires substantial (re)organization, leading to an increase in P600 amplitude. Crucially, the updated utterance representation provides top-down cues to semantic memory, which serve to pre-activate potential upcoming conceptual knowledge. Hence, the RI model thus effectively instantiates a reverberating circuit between retrieval (N400) and integration (P600) processes, where top-down information serves to facilitate bottom-up word processing.

1.1. Role of word association in sentence context

In the present paper, we aim to address an important outstanding issue concerning how abovementioned reverberating dynamics facilitate retrieval. That is, it is assumed that both sentence-level (and discourse-level) contextual priming and lexical priming can lead to the pre-activation of conceptual knowledge in semantic memory. Indeed, this is consistent with the well-known findings that lexical association can lead to a reduced N400 in response to the second word in related word pairs (Kutas, 1993); and that in sentential and discourse contexts, N400 amplitude is inversely related to the cloze probability (CP) of a given word, the percentage of subjects that completed a particular sentence with this word in a sentence-completion task (Kutas and Hillyard, 1984). Yet, it is not clear how these factors interact, as the results of existing studies are contradictory. For instance, some studies (Coulson et al., 2000; E Khachatryan et al., 2014; C Van Petten et al., 1999; C Van Petten & Kutas, 1990) suggest that if a prior context is sufficiently constraining, it can override lexical factors affecting N400 amplitude, such as word-frequency (Van
Petten and Kutas, 1990), or lexico-semantic associations between a target word and a preceding prime (Coulson et al., 2000; E Khachatryan et al., 2014; C Van Petten et al., 1999). In another study, however, Van Petten (C Van Petten, 1993) showed that when the associated and unassociated word-pairs are embedded in syntactically correct pseudo-sentences (anomalous sentences), such as “When the moon is rusted it is available to buy many stars” or the Santa Ana.”, word association has a significant effect on N400 amplitude. Additionally, this study showed that effects of sentence-level context and word association can be additive: smaller N400 amplitudes were observed in response to meaningful sentences containing lexical associates compared to meaningful sentences without associates and meaningless sentences with associates. However, it is unclear whether word predictability, reflected by CP, played any role in the modulation of N400 amplitude, as Van Petten did not report whether she controlled her stimuli for CP. Recently, another study (Chow et al., 2014) suggested that low-level lexical manipulations such as word repetitions and high-level sentence processing such as word predictability can have an additive effect on N400 amplitude. This was also suggested by a number of eye-tracking studies evaluating the interaction between sentence context and word frequency (for a review of these studies, see Staub, 2015). Furthermore, Camblin et al. (Camblin et al., 2007), using both ERP and eye-tracking techniques observed the interaction between lexical associations and discourse congruence, but only in the late stage of the processing: the effect of association in the P600 time-interval was present only for an incongruent context. Here, similar to previously mentioned study, both context congruity and association had an independent effect on N400 amplitude with a significantly stronger effect of congruity.

One of the reasons for the seemingly contradictory results may be that the effects of these factors and their interaction (as in case of (Camblin et al., 2007)) is difficult to disentangle in the temporal domain alone, as they affect retrieval and integration processes at (more or less) the same time (Brouwer and Crocker, 2017). Hence, the spatial dissociation of the mentioned effects seems a reasonable goal. An increasing number of studies show the involvement of right hemisphere in language comprehension (Federmeier et al., 2008; Friederici, 2002). The precise functional role of right hemisphere, however, is currently still unclear. There are two main hypotheses on the processing of semantic and/or lexical information by the two hemispheres. According to one of the hypotheses, linguistic information in the right hemisphere is processed in a “bottom-up” manner whence this hemisphere shows more pronounced processing of the lexical information compared to message-level information. Therefore, according to this hypothesis, the right hemisphere can be considered as partially “message-blind”. Message-level information is then assumed to be mainly processed by the left hemisphere, in a controlled “top-down” manner (Faust, 1998; Faust et al., 2003; Faust and Kravetz, 1998). The alternative hypothesis (Chiarello et al., 2001; Coulson et al., 2005; Federmeier, 2005; Federmeier and Kutas, 1999) suggests that both hemispheres engage in the processing of both message-level and word-level information, but that they contribute differently to the unified sentence interpretation. Coulson et al., 2005 present supporting evidence for the latter hypothesis using scalp-recorded EEG and mono-hemispheric presentation of the stimulus. They embedded associated and unassociated word-pairs, like “olive → oil” and “olive → shoes”, into meaningful (“Italian cook uses too much olive oil.” and “It was hard to walk in her olive shoes.”) and meaningless (“Italian cook uses too much olive shoes.” and “It was hard to walk in her olive oil.”) sentences and presented them to the left or right visual field, assuming that the processing of the lexico-semantic information is constrained to one cerebral hemisphere only, albeit for a short time. They showed that when the target word (here, the last word of the sentence) was
presented in the right visual field (left hemisphere), word association modulated the N400 amplitude only in response to meaningless sentences, whereas when presenting the target word in the left visual field (right hemisphere), word association modulated the N400 amplitude in response to meaningful sentences, albeit to a lesser extent. Although the effect of sentence meaning in both presentations surpassed the effect of word association, it was shown that when narrowing down the visual field of presentation, and whence, shortly constraining the lexico-semantic processing to one hemisphere only, lexical information (word level information) can play a larger role in processing sentence level information, even when the context is constraining (e.g., Van Petten and Kutas, 1990).

To this end, in order to discern the effects of lexical and semantic information in sentence processing in the spatio-temporal domain, we will cross factors of sentence congruity and within sentence word association but instead of recording only scalp EEG responses, as done in other studies, we employ a more direct measure of electrophysiological activity – intracranial EEG. It exhibits both high spatial and temporal resolutions, and hence may offer a window on the retrieval processes underlying the N400 component, as well as a way to discern the brain regions that participate in word association and/or sentence congruity processing.

1.2. Intracranial EEG

Intracranial EEG (iEEG) is an invasive recording method as grids and strips of electrodes are placed directly on the surface of the cerebral cortex (subdural – electrocorticography, ECoG) or implanted in deeper cortical areas, such as, the hippocampal region. These recordings serve a clinical purpose, that is, to pre-operatively localize the source(s) of seizure activity of refractory epilepsy and to do the functional mapping of the eloquent cortex (language, vision, somato-sensory, motor functions, etc.) in patients scheduled for surgical treatment. The advantage of iEEG is the combination of a high spatial resolution (unlike scalp recorded EEG) with a high temporal one (unlike other neuroimaging techniques, like fMRI). It provides the opportunity to study changes in electrophysiological activity over short time intervals and in restricted brain regions. Since it is an invasive procedure and is performed only when serving specific clinical needs, there are not many studies that rely on iEEG recordings. As such, the number of ERP studies investigating language processing and semantic priming in patients with bihemispherical iEEG implants is rather limited (Halgren et al., 1994a, 1994b; Khachatryan et al., 2016; McCarthy et al., 1995; Nobre and McCarthy, 1995). Early iEEG studies on language processing observed the N400 ERP, together with a late positivity (N430-P630 complex) in response to anomalous sentences (McCarthy et al., 1995) and unrelated word pairs (Nobre and McCarthy, 1995), mostly in bilateral anterior medial temporal lobes (AMTL), but later also in a large area of the left temporal cortex (collateral sulcus, parahippocampal sulcus, fusiform gyrus, superior and medial temporal gyri) (Halgren et al., 1994a; Ibanez et al., 2013) and the lingual gyrus (no difference in response to incongruity was mentioned in these regions) (Halgren et al., 1994b). As the N400 source(s), the brain area(s) were taken for which the closest electrodes had a shift in polarity or a dramatic gradient in ERP magnitude (McCarthy et al., 1995; Nobre and McCarthy, 1995; Swick et al., 1994).

1.3. Present study

Based on scalp recorded EEG studies on word versus sentence level information processing and iEEG studies on language processing, we hypothesize that the iEEG technique is suitable for
addressing the question of whether we can spatially dissociate between sentence-level and lexical-level effects on the retrieval processes underlying the N400. That is, the use of iEEG may reveal certain brain areas involved in the processing of word-association in sentence context during word-retrieval (N400) and/or it’s integration (P600). Furthermore, by studying the ERPs of both early (N400) and late (P600) time-windows with the technique of excellent temporal and spatial resolutions, we will be able to investigate how the reverberating circuit of facilitation of word-processing by top-down integration processes occurs. Ultimately, if we observe the effect of sentence congruity on the ECoG electrodes covering the right hemisphere, we will be able to directly challenge the hypothesis that suggests the “message-blindness” of right hemisphere, given that our technique provides direct evidence about the signal generated in particular brain areas rather than indirect evidence about signals transferred from other areas. To our knowledge, our manuscript presents the first insight into the spatial distribution of the lexical information processing in sentence context and reveals different brain areas involved in the processing of sentence and/or lexical level information.

For the current study, we used sentential stimuli consisting of four sentence groups (280 sentences in total) following a 2x2 (sentence congruity x word association) design. Stimuli were visually presented to three patients implanted with invasive EEG. During the experiment, scalp-EEG was simultaneously registered. We further compared the obtained results with the ones from healthy controls of one of our previous studies, that used the same stimuli (Khachatryan et al., 2017).

2. METHODS AND MATERIALS

2.1. Participants
Three patients with refractory epilepsy from Ghent University Hospital, implanted and admitted for an invasive video-EEG monitoring, participated in the study. The demographic and clinical details of the patients can be found in Table S1 in the Supporting Information.
Patients had Dutch as their mother tongue and normal or corrected to normal vision. All patients had normal level of consciousness. The study was conducted according to the current version of the Declaration of Helsinki (2013) following ethical approval from Ghent University Hospital’s Ethical Committee. All participants gave their written informed consent prior to participating in the study and after being informed about the set-up and its goal.

2.2. Materials
Our experimental stimuli proved to be able to evoke an N400 potential, as it was previously used to study language processing in both healthy subjects and patients with aphasia (Khachatryan et al., 2017). Two hundred eighty (280) Dutch sentences were presented to our subjects. The cloze probability (CP) of the original sentences was obtained by asking 40 graduate and undergraduate students from KU Leuven to fill in the best completion of these 280 sentences. The average CP of those sentences for their most frequently supplied completion (which was also the target word we used) was 66.99% (SEM = 1.65). The repeated measure analysis of variance (ANOVA) showed no significant difference between the CP of the original sentences of different sentence groups (F(3, 276) = 0.76, p=0.52). Half of the original 280 sentences were kept congruent and the other half changed into incongruent ones. Incongruent sentences were composed by replacing the final (target) word of the congruent sentence with a word that did not semantically match the context of the sentence, and hence rendered it meaningless. The target words of incongruent sentences were
never reported in our sentence completion task, thus their cloze probabilities were considered equal to zero. In approximately half of both the congruent and incongruent sentences, the association between target and prime (the closest open class word, i.e., noun, verb, adverb or adjective) words were present. In the other half, no association was present. Hence, four sentence groups were created by crossing factors of word association and sentence congruity (Table 1; also note the abbreviations per sentence group for quick referencing). Finally, three Dutch-speaking colleagues, who were blind to the sentence group, independently checked the meaningfulness of the congruent and incongruent sentences.

**Table 1: Exemplar sentences of each sentence group in Dutch and their translation into English (for illustration purposes only).**

<table>
<thead>
<tr>
<th>Sentence group</th>
<th>Example sentence</th>
<th>English translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruent – associated</td>
<td>Ze stak brandhout† in de kachel*.</td>
<td>She put firewood† into the stove*.</td>
</tr>
<tr>
<td>Congruent – unassociated</td>
<td>Met mijn familie heb ik weinig† contact*.</td>
<td>With my family I have little† contact*.</td>
</tr>
<tr>
<td>Incongruent – associated</td>
<td>De operatietafel was bevlekt met etter† en wonde*.</td>
<td>The operational table was covered with pus† and wound*.</td>
</tr>
<tr>
<td>Incongruent – unassociated</td>
<td>De leraar schreef zijn naam† op het meer*.</td>
<td>The teacher wrote her name† on the lake*.</td>
</tr>
</tbody>
</table>

† Prime word
* Target word

The lexical characteristics of the target words were balanced across sentence groups. A repeated measure ANOVA did not reveal any significant difference across sentence groups for word frequencies (F(3, 276) = 0.27, p=0.85) checked with SUBTLEX Dutch frequency database (Keuleers et al., 2010); word length (F(3, 276) = 0.82, p=0.48) or orthographic neighborhood size (OTAN) (F(3, 276) = 0.39, p=0.76), both checked with CLEARPOND (Marian et al., 2012) non-commercial software. The association-strength values between prime and target words for congruent – associated and incongruent – associated sentence groups were taken from the word association database for Dutch word-pairs (De Deyne and Storms, 2008). The average association strength for congruent – associated group was 0.026 (SEM = 0.0089), while for incongruent – associated group it was 0.1537 (SEM = 0.0148). The Student’s t-test showed a significant difference between these two values (p<0.0001).

2.3. Experimental procedure
The experiment was conducted in patients’ hospital rooms at the center for neurophysiology monitoring, Ghent University Hospital, as they were bed ridden during the monitoring period. The experiment was presented as a computerized sentence comprehension test (on semantics) with simultaneous scalp and invasive EEG recording.

Patients were seated in a hospital bed at a distance of approximately 70 cm from the LCD screen of a laptop.
The sentence comprehension test was split into short blocks and participants could take a break every 5 to 7 minutes. During the experiment, sentences were presented on the LCD screen using a rapid serial visual presentation (RSVP) paradigm, that is, one word at a time. The words were presented with white letters on a black background for 500 ms with a jittered interstimulus interval (ISI) of around 350 ms on average (ranging between 200 and 500 ms). The jitter was introduced in order to average out the ERPs from previous words in the sentence. As the jitter was only +/- 150 ms, it did not influence the presentation speed and none of the participants experienced any problems or even noticed any specificity in the presentation. At the end of each sentence (after the target word), a blank screen appeared for 700 ms, followed by a question mark with two options, presented with boxed labels with the words ‘Goed’ (correct) and ‘Fout’ (false). Subjects were asked to indicate by pressing one of the mouse buttons whether the sentence was meaningful or meaningless, as soon as they saw the question mark (delayed button press): with left for meaningful and right for meaningless sentences (semantic anomaly judgment task). After the button-press was performed, feedback was presented on the screen that did not reflect the correctness of the response, but rather aimed at reminding the function of each of the buttons. The button press response was asked from the participants to keep them attentive and to ensure that each word was thoroughly processed. Additionally, although the elicitation of the N400 does not require attention, it is known that an explicit task evokes the N400 of larger amplitude (M Kutas & Federmeier, 2009). The button press was delayed to avoid interference of response related ERPs with the N400 (Van Vliet et al., 2014). Prior to the main experiment, all patients completed a training session of six trials. All stimuli were presented using Matlab’s Psychophysics Toolbox (Brainard, 1997).

2.4. Invasive and scalp EEG acquisition
Scalp EEG was acquired from 27 active electrodes following the 10 – 20 international system. Conductive gel was applied to each electrode in order to improve the contact between electrodes and patients’ scalp. The iEEG signal was recorded using depth and subdural platinum electrodes embedded in silastic (N-Connection for patient P1 and Ad-Tech for patients P2 and P3). The electrode exposure for the subdural grids was 2.3 mm with 4 mm electrode diameter and center-to-center distance 10 or 15 mm. For the depth electrodes, the contact size was 2.4/1.1 mm (overall length/diameter) and 4 mm center-to-center distance. The locations of each subdural grid, strip and depth electrode are listed in table 2. Both scalp and invasive EEG signal was digitized at 1024 Hz sampling rate using the medically certified Micromed digital video compatible EEG recording system.

Table 2: details on the ECoG grids and depth electrode implants locations in patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Electrodes</th>
<th>Location and type of the electrodes and number of electrode contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 (P1)</td>
<td>LTD</td>
<td>dorsal flank of left temporal operculum (depth electrode - 8)</td>
</tr>
<tr>
<td></td>
<td>LPG</td>
<td>left parieto-occipital cortex (subdural grid - 6 × 8)</td>
</tr>
<tr>
<td></td>
<td>LOG</td>
<td>left occipital cortex (subdural grid – 4 × 5)</td>
</tr>
<tr>
<td></td>
<td>LOSA</td>
<td>left apical occipital cortex (subdural strip – 4 ×1)</td>
</tr>
<tr>
<td></td>
<td>LOSB</td>
<td>left basal occipital cortex (subdural strip – 4 ×1)</td>
</tr>
</tbody>
</table>
LTS left lateral posterior temporal cortex (subdural strip – 6 x 1)

<table>
<thead>
<tr>
<th>Patient 2 (P2)</th>
<th>RHD</th>
<th>right hippocampus (depth electrode – 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHD</td>
<td>left hippocampus (depth electrode – 8)</td>
</tr>
<tr>
<td></td>
<td>LTG</td>
<td>left temporal cortex (subdural grid – 4 x 8)</td>
</tr>
<tr>
<td></td>
<td>RTP</td>
<td>right posterior temporo-basal cortex (subdural strip - 4 x 1)</td>
</tr>
<tr>
<td></td>
<td>RTA</td>
<td>right anterior temporo-basal cortex (subdural strip – 4 x 1)</td>
</tr>
<tr>
<td></td>
<td>RTL</td>
<td>right temporo-lateral cortex (subdural strip – 8 x 1)</td>
</tr>
</tbody>
</table>

Patient 3 (P3) LG Left temporal cortex (subdural grid – 4 x 5)

2.5. Localization of ECoG electrodes
For patients P1 and P3, the post-implantation MRI and CT images were co-registered and normalized to MNI space using the Statistical Parametric Mapping (SPM12) toolbox (http://www.fil.ion.ucl.ac.uk/spm/). From the CT images, the locations of the cortical and depth electrodes were segmented using thresholding. The threshold was determined visually for each patient to get an optimal view of the electrodes. Segmentation was refined manually to exclude wires and other artifacts. The center of each segmented electrode was calculated and projected on a template cortical surface (cvs_avg35_inMNI152) provided by Freesurfer (http://www.freesurfer.net/). For patient P2, no post-implantation CT image was available and cortical and depth electrode locations were inferred from the artifact on the post-implantation MRI in MNI space. Not all grid and strip electrodes could be deduced from the artifacts, so interpolation was done to derive the missing locations, taking the implantation scheme into account. Grid and strip electrodes were again projected on the template cortical surface.

2.6. Scalp and invasive EEG data analysis

Scalp recorded EEG: The simultaneous recording of scalp and invasive EEG for research purposes is rare (Ball et al., 2009) due to the suboptimal quality of scalp recorded EEG in these patients because of the long-term monitoring and the influence of incision location and afterwards the scar on the quality of the recording. One of our patients (P2) had an implantation with the minimally invasive technique, which had relatively little influence on the scalp recorded EEG. Therefore, we analyzed the scalp recorded EEG of that patient. The EEG signal was re-referenced off-line to an average mastoid reference (TP9 and TP10) and filtered twice using a 4th order finite impulse response (FIR) filter: once with a low-pass filter with cutoff at 30 Hz and a second time with a high-pass filter with cutoff at 0.3 Hz. Then, the signal was segmented into epochs starting from 100 ms prior to target word onset until 1000 ms post-onset. In order to clean the obtained epochs from artifacts (eye blink, eye movement or conductance impairment), we set an amplitude threshold of +/-70 µV on every electrode. Epochs that had amplitude beyond +/-70 µV at any moment in time were discarded. Only the channels that had 30 or more remaining trials after cleaning procedure were included in the further analysis. The following electrodes survived the mentioned cleaning...
procedure: FT9, F7, Fz, F4, T9, C3, Cz, C4, T10, T5, P3, Pz, P4, T6, Oz and O2. After cleaning the data, baseline correction was applied using the average EEG signal in a 100 ms interval prior to stimulus onset. For the epochs that were kept, the average EEG amplitude in the 300 and 500 ms (early time window – N400) and 500 and 800 ms (late time window – P600) post – onset of the target word was calculated. The scalp recorded EEG of other patients was unusable, due to the influence of swollen and scarred tissues, therefore, those recordings were not considered in our analysis.

**Intracranial EEG:** For the iEEG data, after manually checking the raw signal on the absence of interictal patterns, we re-referenced it off-line to a common average reference (CAR) per grid, strip or depth electrode. The remaining pre-processing procedure was the same as for the scalp recorded EEG data with the only difference being the use of a +/-500 µV amplitude threshold for removing contaminated epochs since the magnitude of iEEG signal can be larger than that of the scalp recorded EEG. Data analysis was performed in Matlab, using the BIOSIG bio-signal processing toolbox (Vidaurre et al., 2011).

### 2.7. Statistical analysis

For the scalp recorded EEG, a repeated measure ANOVA was applied to each electrode with sentence congruity (SC – 2 levels), word association (WA – 2 levels) and their interaction (2×2 design) as fixed effects. To correct for multiple comparisons, the Student’s t-test with Benjamini-Hochberg FDR correction for p-values was applied (Benjamini and Hochberg, 1995). For the iEEG recordings; as a Kolmogorov-Smirnov normality test showed that normality did not apply to all electrodes, each electrode was analyzed individually using the Kruskal-Wallis non-parametric test (McDonald, 2014). As non-parametric tests can manage the evaluation of only one factor for even slightly unbalanced data (small differences between number of trials per sentence group), we started our analysis using sentence group (SG) as a factor with 4 levels representing the full model fit of our (2 × 2) design. Even though the SG factor per se represents a 1 × 4 model, the total fit of 1 × 4 and 2 × 2 models for asymptotic data is the same; therefore, for the total fit, we decided to use this factor. After that, we continued with our analysis by considering factors SC and WA individually. In order to evaluate the possible effect of interaction between SC and WA; we considered the subgroups of the data and separately analyzed the effect of WA in the congruent and incongruent contexts accordingly. The obtained p-values (3 effects – SG, SC and WA) for each electrode were FDR corrected (Benjamini and Hochberg, 1995). Additionally, we performed an FDR correction for multiple comparisons across electrodes that showed significance per effect. The effect was considered statistically significant when the corrected p-value of the test was smaller than 0.05.

### 3. RESULTS

#### 3.1. Behavioral results

As the behavioral data on the semantic anomaly judgement task collected only from patients P2 and P3 was available (the data from P1 was unavailable due to technical issues beyond our control), we further present these results.

Both patients performed significantly above chance level with the average performance for patient P2 being 0.92 and for patient P3 0.85. They performed on individual sentence group with the following accuracies: congruent – associated 0.83 (P2) and 0.71 (P3), congruent – unassociated 0.9 (P2) and 0.83 (P3), incongruent – associated 0.95 (P2) and 0.91 (P3), incongruent – unassociated 1 (P2) and 0.93 (P3). The performance of our patients was comparable to the ones obtained from
healthy subjects in other studies with similar stimuli (e.g., in Khachatryan et al., 2017, it was 0.96, in Chow et al., 2015 0.91, in Kuperberg et al., 2003 0.926, and in Hoeks et al., 2004 0.85). Repeated measure ANOVA with sentence congruity (SC), word association (WA) and their interaction (SC x WA) as fixed effects and the behavioral responses of the individual patients as dependent variable showed that for both patients the effect of sentence congruity was significant (for patient P2 $p=0.0006$, and for patient P3 $p=0.0005$). The effects of neither word association nor SC x WA interaction showed significance for any of the patients (in all cases $p > 0.05$). As patients performed a delayed semantic judgement task, in order to avoid interference of response related potentials with the studied language related ones (Van Vliet et al., 2014), reaction time data was not relevant. Therefore, we did not include that in the analysis.

3.2. Scalp recorded EEG

Before going through the iEEG data, we will discuss the scalp recorded EEG data of patient P2 in order to establish the pattern of our scalp recorded EEG signal in that patient and compare those results with the ones from our previous work with the same stimuli (Khachatryan et al., 2017). Despite its excellent temporal resolution, scalp recorded EEG relies on electrical activity to flow from the neural generator through tissues with different conductivity characteristics (cerebro-spinal fluid, skull and skin) (Freeman et al., 2003) before reaching the recording electrodes, and therefore not only its spatial resolution will be limited but also its amplitude and bandwidth. Intracranial EEG (iEEG) signals perform better in that regard (Miller et al., 2009; Staba et al., 2002) but they come with the certain cost. Firstly, they require surgery, which serves certain medical needs, such as localizing epileptic activity and/or doing functional mapping of eloquent cortex. Secondly, even though iEEG can offer both excellent spatial and temporal resolutions given its implantation area, the grid that records this data covers a limited area of the brain; therefore, we are limited to observing effects evoked only directly under the grid. The joint recording of scalp- and iEEG provides the best of both worlds but it is rarely performed.

As the patients undergo the surgery, the quality of scalp recorded EEG in these patients is suboptimal due to the influence of swollen and scarred tissue and long-term monitoring (several days). As one of our patients was implanted using a minimally invasive technique, the influence of scarred and swollen tissue on the recorded signal was minimal; therefore, we focus on presenting the results of this patient. Here, we were able to track the signal from the neural generators to the scalp. Furthermore, by comparing the results of our patient with the scalp recorded healthy control group, tested with the same stimuli (Khachatryan et al., 2017), we are in a position to evaluate the differences and similarities between these two groups (iEEG implanted epilepsy patient and healthy controls).

We performed repeated measure ANOVA on the 16 scalp-recorded EEG electrodes (FT9, F7, Fz, F4, T9, C3, Cz, C4, T10, T5, P3, Pz, P4, T6, Oz and O2) from patient P2 that survived the cleaning procedure (Fig. 1) using the factors SC, WA and their interaction as fixed effects. In the early time-window (300 – 500 ms) the results showed a similar picture as in the healthy controls of the previous study (Khachatryan et al., 2017): a significant effect of factor SC on electrodes FT9, F7, T5, C3, Cz, Pz, C4, T6, P4, Oz and O2 (e.g., electrode Pz, $F = 12.77$, $p<0.0005$) and no significant effect of WA or SCxWA interaction. The post-hoc Student’s t-test with FDR correction for multiple comparisons showed that the N400 response to both congruent groups (congHA and congLA) was significantly smaller than the one in response to both incongruent groups (incongHA and incongLA) (for electrode Pz, corrected $p < 0.05$ for all mentioned comparisons). No significant difference
between two congruent or two incongruent groups was detected (for electrode Pz, \( p=0.9 \) in both cases). As for the late time window, we observed a significant effect of SC on two electrodes only: FT9 (\( p<0.05 \)) and F7 (\( p<0.0005 \)). For the other electrodes, none of the studied effects showed significance in this time window. The reason for this might be the small number of observations, as we only evaluated one subject (patient P2) and additional noise from the recording (caused by swollen tissues and the scar) covering the small possible effect that is visible in the control group in Khachatryan et al. (2017) during this time window.

![Figure 1: ERP response from scalp-recorded EEG for patient P2.](image)

The presented electrode positions are highlighted in grey on the scalp. Only the presented 16 electrodes remained after cleaning the data from artifacts that cross the 70 \( \mu \)V threshold. The areas with a significant effect of congruity are shaded.

Similar to some previous studies that used a highly constraining context (e.g., Van Petten et al., 1999, Coulson et al., 2000), the study of scalp recorded EEG signal from our iEEG implanted patient showed a significant effect of SC but no effect of WA or SC \( \times \) WA interaction. Thus, we suggest that for sentences with highly constraining context, it is difficult to disentangle lexical and contextual effects using only scalp recorded EEG.

### 3.3. Intracranial EEG recording

Depending on the patients’ level of fatigue and their request to stop the experiment we had different durations of experiment for each patient, and therefore, different number of epochs per patient (table 3).

#### Table 3: number of epochs for each patient per stimulus group

<table>
<thead>
<tr>
<th>Patient</th>
<th>congHA</th>
<th>congLA</th>
<th>incongHA</th>
<th>incongLA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
We then mapped the iEEG electrodes of each subject onto their unique anatomical locations in the brain (Supporting information, for all the channels mapped to both hemisphere) and studied the effects of factor sentence group (SG) on amplitude of early and late time – windows using the Kruskal-Wallis non-parametric test, which would reflect a general model fit. Afterwards, we evaluated the effects of individual factors SC and WA on the amplitude of early and late time windows using the same test. In order to evaluate the interaction between these two factors, we studied the effects of WA in the subgroups of observations, therefore, evaluating this effect in the meaningful and meaningless contexts accordingly. Eventually, as our P1 patient had smallest number of observations per stimulus group, we conducted a bootstrapping analysis to show that the number of trials in this patient is enough to observe a significant effect.

**Effect of SG:** For the early (300 – 500 ms) time window, the Kruskal-Wallis non-parametric test showed a significant effect of SG mainly for the left temporal cortex (observed in both P2 and P3 patients implanted with grids in left temporal cortex), mostly on superior and middle temporal gyri and superior and inferior temporal sulci (Fig. 2 for the effect locations for patient P2, Fig. 3 - for patient P3 and table 4). For both patients the effect of SG during the early time window (300 – 500ms) was located in the middle part of temporal cortex (superior and middle temporal gyri).

For the late (500 – 800 ms) time window, the effect of SG was more bihemispherically distributed with significance on several electrodes on the left temporal cortex (mainly observed in patient P2), left and right hippocampi (P2, Fig. 4), right temporal (P2, SI, Fig. S2) cortex, and small areas on left parietal (P1, SI, Fig. S3) and left occipital cortices (P1, SI, Fig. S5), (table 4).

### Table 4: Number of electrodes (N), Chi square and p – value of sentence group (SG) effect using Kruskal – Wallis test for early (300 – 500 ms) and late (500 – 800 ms) time windows. SEM = standard error of the mean.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Left temporal (P2 &amp; P3)</th>
<th>Right temporal (P2)</th>
<th>Left hippocampus (P2)</th>
<th>Right hippocampus (P2)</th>
<th>Left parietal (P1)</th>
<th>Left occipital (P1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>66</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>48</td>
<td>28</td>
</tr>
</tbody>
</table>

**Effect of SG 300 – 500 ms**

<table>
<thead>
<tr>
<th>N</th>
<th>15</th>
<th>1</th>
<th>--</th>
<th>--</th>
<th>--</th>
<th>1</th>
</tr>
</thead>
</table>

| Chi sq. (SEM) | 16.2 (4.33) | 8.95 | -- | -- | -- | 17.1 |

| P (SEM)       | 0.0082 (0.0077) | 0.0388 | -- | -- | -- | 0.0072 |

**500**

<table>
<thead>
<tr>
<th>N</th>
<th>11</th>
<th>7</th>
<th>8</th>
<th>8</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
</table>
Figure 2: Electrode locations of subdural grid on left temporal cortex and the ERP image (patient P2). The time ranges on the electrodes that show significance of SG effect are shaded. The red rectangle indicates the electrodes with significant gradient in amplitude.
Figure 3: Effect locations on left temporal cortex and ERP image for patient P3. The time ranges on the electrodes that show significance of SG effect are shaded.

Effects of individual factors (SC and WA): Here, we evaluated the individual effect of sentence congruity (SC) and word association (WA) on amplitudes of ERPs in the early (300 – 500 ms) and late (500 – 800 ms) time windows. For the early time window, a significant effect of SC was present mainly in left temporal cortex (17 electrodes patients P2 and P3) and on only one electrode in left parietal cortex (P1). The effect of WA (Fig. 5) for this time window was significant on one electrode in the right hippocampus and two electrodes in the right temporal cortex (both cases, P2).
Figure 4: Depth electrode locations and ERP images for left and right hippocampi for patient P2. Red rectangles show the neighboring electrodes on which the polarity shift was observed.

For the late time window, similar to the SG factor, the effects were spread more bi-hemispherically with a significant effect of SC on 13 electrodes in left temporal cortex (P2 and P3), 8 electrodes in left and 7 electrodes in right hippocampi (P2), 5 electrodes in right temporal cortex, 2 electrodes in left parietal and one electrode in left occipital cortices (both cases, P1). The effect of WA was significant on 2 electrodes in left temporal cortex (P2), 3 electrodes on left and 7 electrodes on right hippocampi, 2 electrodes in right temporal cortex and 1 electrode in left parietal cortex (Fig. 5). Table 5 presents the effects of SC, WA and SG on each of the ERP components (N400 and P600) according to the anatomical locations of the electrodes.

Table 5: Anatomical distribution of effects of fixed factors (SC, WA and SG) on ERP in early (N400) and late (P600) time windows.

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>N400 (300 – 500 ms)</th>
<th>P600 (500 – 800 ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left temporal cortex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus (MTG) (P2, P3)</td>
<td>SC, SG</td>
<td>SC, WA (middle MTG), SG</td>
</tr>
<tr>
<td>Anterior temporal lobe (ATL) (P2)</td>
<td>SC, SG</td>
<td>SC, SG</td>
</tr>
<tr>
<td>Inferior temporal gyrus/sulcus (ITG/ITS) (P2, P3)</td>
<td>SC, SG</td>
<td>SC, WA (anterior ITG), SG</td>
</tr>
<tr>
<td><strong>Hippocampi (P2 - Hp)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>--</td>
<td>SC, WA (less), SG</td>
</tr>
<tr>
<td>Right</td>
<td>WA (posterior Hp)</td>
<td>SC, WA, SG</td>
</tr>
<tr>
<td><strong>Left parietal cortex (P1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior parietal cortex (IPC)</td>
<td>SC (very local)</td>
<td>WA, SG (in both cases angular</td>
</tr>
</tbody>
</table>
### Table: Electrode Positions and ERP Images

<table>
<thead>
<tr>
<th>Region</th>
<th>Electrodes</th>
<th>Condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior parietal cortex (SPC)</td>
<td>---</td>
<td>SC, SG</td>
</tr>
<tr>
<td><strong>Right temporal cortex (P2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>WA, SG</td>
<td>SC, WA, SG</td>
</tr>
<tr>
<td>Posterior middle and inferior temporal gyri</td>
<td>---</td>
<td>SC, SG</td>
</tr>
<tr>
<td>Anterior inferior temporal sulcus</td>
<td>WA</td>
<td>WA, SG</td>
</tr>
<tr>
<td><strong>Left occipito-parietal cortex (P1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parieto-occipital junction (POJ)</td>
<td>SG</td>
<td>SC, SG</td>
</tr>
</tbody>
</table>

---

**Figure 5:** Electrode positions and ERP images for locations that show an effect of WA independent from effects of SC or SG.

**Effect of WA in the meaningful and meaningless contexts:** As we needed to use a non-parametric test (due to the absence of normality, see section 2.7.), we could not evaluate more than one factor at a time. Whence, we investigated the total model fit using factor SG (1 x 4) that has the same total fit as for a 2 x 2 design. Furthermore, in order to study the possible effect of WA x SC interaction on ERP amplitudes in both early and late time windows, we split the data into two subgroups and evaluated the effect of WA separately in congruent and incongruent contexts.

Here, for the early time window (300 – 500 ms) the effect of WA in the congruent context was significant only for one electrode on left parietal cortex (P1, electrode LPG36, p=0.019) and one electrode on left occipital cortex (P1, electrode LOG14, p=0.048). In the incongruent context, the effect of WA in this time window was relatively larger and more widespread: significant on 8
electrodes over left temporal cortex (P2), 2 electrodes in left and one in right hippocampi (both P2), 2 electrodes in right temporal (P2) and 2 electrodes in left occipital (P1) cortices.

For the late time window (500 – 800 ms), the effect of WA in the congruent context was significant mainly in right hemisphere with 3 electrodes on right hippocampus and one electrode in right temporal cortex. Only one electrode on left parietal cortex (LPG36, patient P1 – p=0.0004) showed significance of WA in the congruent context. For the incongruent context, the significant effect of WA in this time window was shown for 7 electrodes in left temporal cortex (P2), 3 electrodes in left and 6 electrodes in right hippocampi, as well as 3 electrodes in right temporal (P2), 2 electrode in left parietal (P1) and 2 electrodes in left occipital (P1) cortices.

**Bootstrapping analysis:** For patient P1 we had the lowest number of electrodes on which we observed significant effects and even then, they were closer to our significance threshold of 0.05 compared to other patients. Since she also had the lowest number of epochs, the observed small effects should be interpreted with caution. In order to ensure that the number of epochs in this patient was enough to detect a significant effect, we bootstrapped the results of one of the grids (p values in response to SG factor) of patient P2 (grid LTG) with the minimum number of trials of P1 (37 trials per stimulation group) using 100 iterations. We showed that, in most of the cases, the effect of SG remained significant (for a comparison of p values before and after bootstrapping, see Supporting Information (SI), Fig. S1). Based on our results (SI, Fig. S1), we could say that the small number of trials cannot be a reason for the spatially constrained significance. Rather, this observation can be explained by the limited involvement of these brain areas in processing of lexico-semantic information given our stimulation paradigm.

In summary, in early time window (300 – 500 ms), the effect of SG and SC was more pronounced in left temporal cortex, while in the late time window (500 – 800 ms) these effects were spread across both hemispheres with involvement of both left and right hippocampi. Unlike scalp recorded EEG of both healthy subjects from (Khachatryan et al., 2017) and patient P2, using iEEG we observed significant effect of WA as an independent factor, as well as in both congruent (although significantly less) and incongruent contexts in both time-windows. The last two can reflect the effect of SC × WA interaction. The effect of WA was mainly observed in late time window and was more pronounced in right hippocampus.

For both time windows, we observed an inverse in polarity (e.g., Fig. 4, electrodes LHD4→LHD5 and RHD3→RHD4) of the potentials, and/or a large gradient in the amplitudes between neighboring electrodes (e.g., Fig. 2, electrodes LTG12→LTG13) in all areas presented with significant effect of evaluated factors. This indicates the potential presence of ERP generators (N400 and/or P600) in those areas (McCarthy et al., 1995).

4. **DISCUSSION**

The goal of the current study was twofold: first we wanted to see if there are brain regions that participate in the processing of word association (lexical information) in sentence context independent of or in addition to the processing of sentence level information and to pinpoint those regions given our bi-hemispherical implantations. Secondly, we wanted to investigate the interaction between bottom-up word recognition and top-down controlled processes. More
specifically, we wanted to disentangle those processes in the spatial and temporal domains given the combination of excellent spatial and temporal resolutions of intracranial EEG recording.

4.1. Lexical versus sentence level information

In the scalp EEG recording of patient P2, we observed only the effect of SC and no effects of WA or SC × WA interaction in both time-windows. This observation is in line with some of the previous studies (Coulson et al., 2000; Khachatryan et al., 2017), while other studies did observe an effect of WA independent of or in interaction with the effect of SC (Camblin et al., 2007; Chow et al., 2014, for review see, Ledoux, Camblin, Swaab, & Gordon, 2006). The difference between these results is probably due to the use of stimuli with different levels of semantic constraints. For instance, unlike the current study, as well as the one of Coulson et al. (2000), Camblin et al. (2007) used discourses with moderate to mild semantic constraint (average CP was 36.9%). On the other hand, Van Petten et al. (1999), similar to our study, used highly constraining sentences (CP ~ 71%) and did not observe effect of WA on N400 amplitude. However, unlike us, Van Petten et al. (1999) did observe an effect of WA in late time-window (P600) in scalp-recorded EEG, which was explained with an attempt to re-analyze the incoming information. We did not observe this effect in scalp EEG, which can be due to the extra constraint caused by semantic judgement task we employed.

Indeed, unlike the scalp recorded EEG signal, in the intracranial EEG signal, all investigated effects (SC, WA and their interaction, expressed with the effect of WA in meaningful or meaningless contexts) showed significance. When comparing our study to previous studies on “mono-hemispheric” processing of similar stimuli (Coulson et al., 2005), in both studies, the significant effect of association was observed. As Coulson et al. (2005) did not have the precision in terms of spatial resolution that we can afford using intracranial EEG recording; they only separated the mentioned effects in terms of hemispheres. Additionally, they did not observe the independent effect of WA neither in early (300 – 500 ms) nor in late (500 – 900 ms in their experiment) time windows, assuming that word-associations cannot be processed independently in the sentence context. Furthermore, when the stimulus is presented in only one visual hemi-field, the information can transfer from one cerebral hemisphere to the other by associative connections between two hemispheres (e.g., corpus callosum), therefore, it is not very clear, whether the effect observed during the experiment with hemi-field presentation is due to the signal that was transferred to that area or generated there. Using intracranial EEG recording and given our available grids, we managed to pinpoint the areas involved in the processing of sentence level information (congruity) and word association independently (Fig. 5), additively (Fig. 4), or in the meaningful and meaningless context as the interaction between these two factors (Fig. 2). We showed that left temporal cortex participates in the processing of sentence congruity independently and with the additional influence of word association, but not word association independently (in sentence context). On the other hand, hippocampi (especially the right one), together with right temporal and left parietal cortices participate in the processing of both sentence-level and word-level information, but depending on the areas - to different degrees. More specifically, the effect of word association was more significant in the right hippocampus and was spread more extensively than in the left one (7 electrodes in right hippocampus versus 3 electrodes in the left one). This effect was also significant on the small areas in the left angular gyrus (LPG34), right inferior temporal sulcus (RTA1), and right posterior superior temporal gyrus (RTL2). This observation additionally challenges the hypothesis concerning the “message-blind” right hemisphere, as both congruity and word
association effects were observed in the right hemisphere. On the other hand, we should pinpoint that the effect of WA (especially independent one) was more pronounced in the right hemisphere compared to the left one. This supports the idea that right hemisphere is prone to processing both message-level and lexical-level information, while left hemisphere relies mainly on message-level information with the additional contribution from lexical-level information, but not the latter one alone.

4.2. The effect of top-down controlled processes on word retrieval

Concerning our second goal, we showed that the bottom-up word recognition and top-down control processes indeed overlap both temporally and spatially. Semantic retrieval, which according to retrieval-integration model (Brouwer and Hoeks, 2013) is reflected in N400, consists of interactions between top-down controlled predictions based on available context (both semantic and syntactic in case of sentences) and bottom-up automatic spreading activation from each presented word (Davey et al., 2015). Thus, the retrieval of word-associated conceptual knowledge is facilitated by a complex interaction between semantic relatedness, lexical association, lexical similarity (feature overlap), and top-down context. The level of influence of each of these factors, as well as their interactions may vary depending on a number of factors, including stimuli, experiments, etc. If the context is strong, such as in high constraining sentences, the context-mediated prediction prevails over automatic spreading activation, leaving only a minor effect of WA in the early time window (N400). Our results show that, in highly constraining stimuli, semantic retrieval is mainly driven by the context-based prediction with little modulation by lexical association. Therefore, based on this observation, we can explain the results of the previous studies (Camblin et al., 2007; Van Petten, 1993), that is, the effect of lexical association on word retrieval comes forward when the effect of sentence meaning is eliminated or attenuated.

In addition to an N400 effect, our data from EEG also revealed a P600 effect. Incongruent sentences had larger P600 amplitudes than congruent ones. This SC induced effect on P600 amplitude is in line with the recent literature on “Semantic P600” effect (see Bornkessel-Schlesewsky & Schlesewsky, 2008; Brouwer et al., 2012; Kuperberg, 2007 for reviews). In this case, semantic anomalies such as “De speer heeft de atleten geworpen” (lit: ‘The javelin has the athletes thrown’) produce a P600-effect, and importantly, no N400 effect, relative to a non-anomalous control “De speer werd door de atleten geworpen” (lit: ‘The javelin was by the athletes thrown’). This finding has spawned a whole spectrum of hypotheses about the functional underpinning of the P600, ranging from traditional syntactic processes to processes of conflict resolution. Yet, what the proposed accounts have in common is that they assume the P600 to arise due to a conflict between multiple processing streams. Crucially, Brouwer et al. (2012) have argued on the basis of a critical review of these multi-stream models, that such models run into trouble when facing the biphasic effects produced in response to semantic anomaly, such as “De speer heeft de atleten opgesomd” (lit: ‘The javelin has the athletes summarized’) relative to the non-anomalous control. Instead, they proposed the single-stream retrieval-integration account, on which P600 amplitude reflects the processing involved in integrating retrieved word meaning into the unfolding utterance representation. In the current study, on some ECoG electrodes, as well as on the scalp-recorded EEG from the control group from Khachatryan et al. (2017), we observed biphasic (N400 – P600) effect in response to both groups of incongruent sentences compared to congruent controls, which could be explained with the difficulty of integration of retrieved concept in the active context.
The reverberating dynamics between the retrieval (~N400) and integration (~P600) processes shed light on the pattern of effects in the late-time window as observed in the current study. That is, given that the left temporal cortex is predominantly involved in a network for semantic retrieval (e.g., Binder et al., 2009; Bookheimer, 2002; Cabeza and Nyberg, 2000; Dronkers et al., 2004; Ellen F. Lau et al., 2008; Turken and Dronkers, 2011, among others), we take the pattern of effects in the late-time window in this area to be driven by controlled-retrieval, facilitating the successful integration of the current word into the unfolding utterance representation. After the initial semantic retrieval of word-associated conceptual knowledge, the mismatch between sentence-level and word-level information leads to the controlled retrieval of additional word-associated conceptual features in order to arrive at a cohesive utterance representation. This process leads to the difference in responses to sentence groups with and without associations in the certain brain regions and the observed significant effect of word association (WA) and SC × WA interaction in those brain areas in the late time window. The spread (more bihemispheric and on the wider areas) of this intensification is logical considering the processes that should be involved in the attempt to reformulate the context and to fix the retrieval. Hippocampi are known to be involved in the working memory update (Preston and Eichenbaum, 2013) and maintenance (Leszczynski, 2011). As the process of the controlled retrieval would include the update of the mental representation and the maintenance of presented information in the working memory, the involvement of these regions in the mentioned intensification would be logical. Additionally, the angular gyrus (Seghier, 2012) actively participates in the process of attention allocation, therefore, the process of controlled retrieval can also benefit from the involvement of this brain region. Recently, Lau and colleagues (Lau et al., 2014, 2013) observed activation in left anterior temporal cortex (ATL) in response to both controlled, predictive word processing in the semantic association paradigm, and in a masked sentence processing paradigm (which they assumed to be a result of automatic activation) using magneto-encephalography. They suggested that left ATL is involved in the both automatic word processing and the generation of predictions in semantic retrieval. We observed the effect of both sentence congruity and SC × WA interaction (effect of WA in the meaningless context) in the left ATL, but no independent effect of WA. Therefore, we can assume that this area indeed participates in the generation of the predictions for semantic retrieval and in the attempt to improve (top-down controlled process) this retrieval in case of mismatch, but it does not participate in the processing of word-association based on spreading activation, at least in the sentence context. This will be in line with the previous suggestion of the controlled processing for sentential stimulus including in masked condition (Dalatrozzo et al., 2012). Finally, our observation of ERPs in both early (N400) and late (P600) time windows in left temporal cortex goes along with number of other studies that were localizing these ERPs, in part, in left temporal cortex using different neuroimaging techniques (EROS and MEG) (Kwon et al., 2005; Service et al., 2007; Tse et al., 2007).

4.3. Propagation of the signal

The EEG technique has an excellent temporal resolution, and it can track changes in brain electrical activity with millisecond precision. Despite this, there are certain brain areas (specifically, deep sources), from which electrical activity is particularly difficult to gauge with scalp EEG. For example, (Megevand et al., 2014) only recently managed to record inter-ictal spikes coming from hippocampus only by using high density EEG (128 – 256 electrodes) recordings. Furthermore, (Dalal et al., 2013) captured the signal from hippocampus with magneto-encephalography (MEG) using a
complicated analysis technique, such as beamforming. The most probable reason for the difficulty to record hippocampal signal is the structure of the hippocampus itself (folding, which leads to closed field activity, therefore, cancelled signal) and its deep location, possibly concealed by other active regions. Since the main effect of WA in our study was coming from both hippocampi, this could explain the absence of this effect in our scalp EEG recordings. Besides hippocampi, we also had other brain regions revealing an (albeit smaller) effect of WA or WA × SC interaction. We assume that as the signal needs to propagate through tissues with relatively low conductance (skull, dura mater, skin, etc.), the size of effects diminishes and therefore, the small effects might not be detectable in our scalp EEG recordings. Another possible explanation for the absence of WA effect in the scalp-recorded EEG can be a differential spatial distribution of this in essence weak effect across subjects. Thus, in our control group, when averaging across subjects, this effect might be cancelled out and the remaining effect not be strong enough to be visible in our scalp-recorded EEG data. In summary, the absence of WA and WA × SC effects in scalp-recorded EEG in our study can be explained with structural specificities of their generators, locations, differential spatial distributions across the subjects and the relatively low strength of the effects.

4.4. Strengths and limitations of the current study

The main weakness of the current study is the unequal distribution of electrodes across the hemispheres, as we have much smaller sample of cortex in right hemisphere compared to left one. As the intracranial grids are implanted exclusively based on the medical indication, we cannot choose the electrode locations; therefore, for future studies we will seek patients with implantations in the right hemisphere to compare with the current study.

We need to refer to our results with caution, since we considered our iEEG patients as multiple case studies and evaluated each electrode separately. This is a common practice in iEEG studies, as even a minimal difference in electrode positions between subjects might lead to a difference in the observed results (Travis et al., 2013). A strong confirmation of this point can be found in (McCarthy et al., 1995) and (Halgren et al., 1994a): even though they evaluated over 60 implanted patients, they still considered each electrode of each subject as a unique entity and did not average over electrodes or over subjects. Another caution is the possible influence of patients’ pathology (epilepsy and 1 patient (P3) with tumor as causing factor) on our results, as some previous studies observed prolongation in the ERP latency in scalp-EEG of epileptic patients (for review, see (Kaga et al., 2013)). The ERP latencies in scalp-recorded EEG from our patient P2 were similar to the ones from healthy subjects, as well as, we did not detect any inter-ictal patterns in the data, thus, the potential influence of epilepsy pathology on our conclusions could be regarded as negligible. Furthermore, the behavioral performance of two patients was similar to that of healthy individuals of some previous studies using similar stimuli (Hoeks et al., 2004; Kuperberg et al., 2003), which can serve as an additional confirmation of our point.

One of the advantages of our study was the ability to evaluate the EEG scalp recordings of one of our patients (P2). We observed the scalp recorded EEG responses similar to those of the control group of our previous study with the same stimuli (Khachatryan et al., 2017). Furthermore, using this data, we managed to evaluate the process of EEG signal propagation through the tissues (dura mater, skull, skin, etc.) and the changes the signal undergoes on the way to the surface.
One could question whether our word association manipulation is too weak to produce a significant effect. This could explain the observed very small WA effect in the congruent context, as here; the average word-association value was significantly smaller compared to the one in incongruent context. However, the observed WA effect in our intracranial recordings for the incongruent context, while absent in the scalp recorded EEG from the same patient provides us with evidence on the value of WA in processing constraining sentences. We could have not obtained this from scalp EEG only. Furthermore, in one of our previous studies (Van Vliet et al., 2014), it was shown that a word association value of 0.03 (similar to ours for congruent context) is enough to evoke N400 potential smaller than the one in response to unrelated word-pairs. Additionally, it is noteworthy that similar to us, Coulson et al. (2005) also observed a significantly smaller effect of WA in congruent context compared to the incongruent one.

Another concern could be with the relatively long stimulus onset asynchrony (SOA) we used. We chose a relatively long SOA, such that the processing of the linguistic information would be strategic (Hill et al., 2005). However, as it was previously mentioned (E F Lau et al., 2008), the SOA in sentence processing does not play a significant role, since the prediction of the upcoming word (target word in our case) is generated during the development of the context. Based on previous studies (Coulson et al., 2005; Van Petten, 1993; Van Petten et al., 1999), as well as our own results, we can assume that, independent of the experimental condition, while processing constraining sentences, context level information always prevails over lexical level information (but not necessarily overrides it). Here, we showed that some brain regions (particularly right hippocampus) process both contextual and lexical information additively, and other regions reflect the interaction of these two (left temporal cortex). Thus, the contribution of lexical level information we observe in several studies (Camblin et al., 2007; Chow et al., 2014; Coulson et al., 2005) most probably comes from the brain regions that are activated to different degrees, depending on, for instance, level of predictability of the stimuli or task of the experiment. As for observed late ERP picture, since the task was used for every sentence in the stimulus set, it is unlikely that our differential ERP results in the late time window (P600) could be caused by the preparation for task performance. Furthermore, the ERP which would have been evoked in response to task performance (Bereitschaftspotential) is normally related to motor activity and is not present in the areas we investigated (Shibasaki and Hallett, 2006).

Our results might also shed light on deficits in patients suffering acute language disorders (e.g., post-stroke aphasia). We showed that certain brain areas (e.g., bilateral hippocampi and right temporal cortex) participates in the processing of word-associations in sentence context in addition to the processing of contextual congruity, whereas others (the temporal cortex) are more involved in the processing of sentence meaning and their interaction. Hence, retrieval processes in patients with impairment of left temporal areas (in particular the superior temporal sulcus and middle temporal gyrus) might rely more on word association than on sentence context. Rehabilitation programs, therefore, might include the training of association-driven comprehension.

In summary, our findings showed that ERPs in both early (N400) and late (P600) time-windows in response to linguistic stimuli are present bi-hemispherically. Similar to some previous studies (Kwon et al., 2005; Tse et al., 2007), we localized N400 mainly to the left temporal cortex (middle and superior temporal gyri and inferior and superior temporal sulci), given the available grid implants. Here, the late time-window ERP presented the intensification of word retrieval, which was
mediated by the top-down controlled process and was attempted to lead to the successful integration. This process, as we discussed above included several brain areas, but was mainly concentrated in hippocampi in both hemispheres. In addition, we found specific localized brain regions in mentioned areas to participate in the processing of word association in sentence context in addition to or independent from processing of sentence level information. Such results would not be possible to observe by conventional neuroimaging techniques due to their restrictive spatial (EEG) or temporal (fMRI) resolutions.

5. ACKNOWLEDGEMENTS.

EK is supported by research grant received from the Belgian Fund for Scientific Research – Flanders (G0A0914N). MMVH is supported by research grants received from the Financing program (PFV/10/008), an interdisciplinary research project (IDO/12/007), and an industrial research fund project (IOF/HB/12/021) of the KU Leuven, the Belgian Fund for Scientific Research – Flanders (G08314N, G0A0914N), the Interuniversity Attraction Poles Programme – Belgian Science Policy (IUAP P7/11), the Flemish Regional Ministry of Education (Belgium) (GOA 10/019), and the Hercules Foundation (AKUL 043). HB is supported by the Cluster of Excellence “Multimodal Computing and Interaction” awarded by the German research foundation (DFG).

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Highlights

- The brain mapping of sentence comprehension is still in progress;
- Invasive EEG provides the combination of high spatial and temporal resolutions;
- We mapped semantic processing of sentences on the left temporal cortex;
- Certain brain areas process word-associations independent of sentence meaning;
- Scalp and invasive EEGs combined shows propagation of EEG signal through tissues.