

A cortical network for semantics: (de)constructing the N400

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Abstract | Measuring event-related potentials (ERPs) has been fundamental to our understanding of how language is encoded in the brain. One particular ERP response, the N400 response, has been especially influential as an index of lexical and semantic processing. However, there remains a lack of consensus on the interpretation of this component. Resolving this issue has important consequences for neural models of language comprehension. Here we show that evidence bearing on where the N400 response is generated provides key insights into what it reflects. A neuroanatomical model of semantic processing is used as a guide to interpret the pattern of activated regions in functional MRI, magnetoencephalography and intracranial recordings that are associated with contextual semantic manipulations that lead to N400 effects.

Event-related potentials (ERPs). Electrical potentials that are generated in the brain as a consequence of the synchronized activation of neuronal networks by external stimuli. These evoked potentials are recorded at the scalp and consist of precisely timed sequences of waves or 'components'.

Morpheme

The smallest linguistic unit that has a specific meaning or syntactic function. For example, the word 'outplayed' consists of three morphemes: 'out', 'play' and 'ed'.

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The recording of event-related potentials (ERPs) has been critically important for the study of language, and particularly informative about its neural basis. Several ERP responses have been studied in the context of research on speech and language. The N400 response — first and most famously¹ noted as an increased negativity in response to semantic violations such as 'I like my coffee with cream and socks' (FIG. 1) — has been studied extensively and has formed the basis of a rich and controversial body of literature. Studies that focus on the N400 response are of broad interest because the experimental designs tap into core aspects of language comprehension.

There are two major components of language processing: accessing long-term memory representations (such as words or morphemes) and integrating these representations into the current semantic, syntactic and discourse structures. Many of the factors that are thought to affect access and integration also affect the amplitude of the N400 response. Earlier papers^{2–8} have articulated different interpretations of the N400 response, largely based on electrophysiological data. Other reviews have highlighted the fact that the linguistic manipulations that modulate the N400 response are associated with activity in a number of different brain regions⁹. In this article we aim to show that such localization data, when considered together with current neuroanatomical and psycholinguistic models of semantic processing, give us insight into both the functional interpretation of the N400 response and the broader network that is involved in processing words in context. We first describe existing hypotheses of the N400 effect — the modulation of the

amplitude of the N400 response by certain experimental paradigms — and review evidence for a functional anatomic model of semantic processing in language. We then test the predictions of this model by considering the localization data from N400 paradigms, with a special focus on the evidence from neuroimaging. In bringing localization data from different recording methods to bear on the functional interpretation of an ERP component, this Review of the N400 response addresses a major challenge that cognitive neuroscience currently faces: how can we combine data from electrophysiological and neuroimaging techniques when the data are so different? In the face of significant variation in spatial resolution and time course, simply aligning the results of different metrics for a given experimental paradigm seems unjustified. Our Review suggests a more promising approach: guided by a psycholinguistic model, we delineate systematic patterns that emerge from diverse measures and experimental manipulations.

The N400 effect

Background: modulation of the N400 response. The N400 response is a broad negative deflection of the ERP that starts 200–300 ms after a word has been presented auditorily or visually and peaks after approximately 400 ms (FIG. 1). Although the N400 response is often associated with semantic anomaly, it can be elicited by most meaningful stimuli, including isolated words^{10,11}, pronounceable non-words (such as 'blicket'; also known as pseudowords)^{10,12}, faces^{13,14} and pictures^{15–17}. This Review does not aim to account for the multiple neural processes

that probably give rise to this component of the ERP waveform³. Instead, we focus on understanding the functional significance and anatomical basis of modulations in the amplitude of the response that are driven by the context in which stimuli are presented.

Two paradigms are frequently found to alter the size of the N400 response. The semantic-priming paradigm involves the presentation of a related or unrelated word before a word target (such as 'coffee-tea' or 'chair-tea'). The semantic-anomaly paradigm involves the presentation of a congruous or incongruous word as a continuation of preceding sentential material (such as, 'I like my coffee with cream and sugar/socks'). In both paradigms, the condition in which the context is 'semantically supportive' elicits a response of smaller amplitude in the 300–500 ms interval¹¹. Although the effects of sentential context on the N400 response tend to be bigger in magnitude, the latency and spatial distribution of the effects of the two paradigms are similar and are assumed to represent the same underlying response¹⁸. Collectively, we refer to this modulation of N400 amplitude as the 'N400 effect'.

The amplitude of the N400 response that is elicited by words in sentential contexts is modulated not only by the degree of anomaly *per se*, but also by predictability. Less expected sentence endings generate a larger N400 response than highly expected ones, even when both endings are semantically congruent (for example, 'I like my coffee with cream and honey' would generate a larger N400 response than 'I like my coffee with cream and sugar')¹⁹. More strikingly, the response to anomalous endings is modulated by the relationship of the target word to the 'expected' ending: an anomalous ending that shares semantic features with the most contextually predicted ending (for example, 'I like my coffee with cream and salt') would produce a smaller N400 response than an ending that is not semantically related to the predicted ending (for example, 'I like my coffee with cream and socks')^{19,20}.

The integration view of the N400 effect. One longstanding view of the N400 effect is that it reflects the process of semantic integration of the critical word with the working context^{1,7,21,22}. According to this interpretation, the effect results from a combinatorial process — integration with previous context — and not from 'simple' lexical-level processes. N400 response amplitude is greater in semantically anomalous sentences because integration is easier in congruent contexts, whereas it requires work to process an implausible continuation in a way that fits the discourse context or prior world knowledge. This view can also explain the finding that non-anomalous, less expected endings produce larger N400 responses than more expected endings (integration is suggested to be more difficult when expectations are not met than when they are met) and the finding that semantic priming results in N400 effects (the priming word is considered the 'context' into which the target word must be integrated). The view that the N400 effect reflects post-access mechanisms is appealing because it can be argued that the N400 response occurs too late to reflect lexical access^{23–25}. Furthermore, early studies

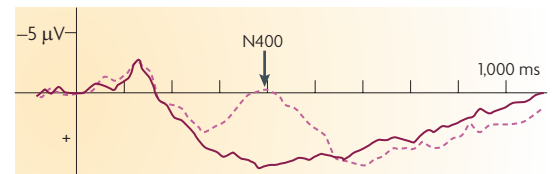


Figure 1 | The standard N400 effect in sentential context. The average event-related potential (ERP) ($n = 10$) recorded from a central midline electrode following the onset of the critical final word in visually presented sentences in which the final word is strongly predicted by the rest of the sentence, as in: 'I like my coffee with cream and sugar.' The strength of this prediction is determined by a 'Cloze procedure', in which participants are asked to provide endings to sentence contexts. The solid line shows the response to predicted endings, such as 'sugar', and the dotted line shows the response to unpredicted, semantically incongruent endings, such as 'socks'. The arrow indicates the N400 component, which is clearly more negative for the incongruent ending. The strength of the N400 effect — the difference between predicted and unpredicted endings — is inversely related to the contextual expectancy of the incoming word.

failed to show any change in the N400 amplitude when the prime was masked below conscious perception²².

The lexical view of the N400 effect. Alternatively, it has been postulated that the N400 effect reflects facilitated activation of features of the long-term memory representation that is associated with a lexical item^{2,26}. According to this theory, the difference between the effects of anomalous and predictable endings arises not because of the anomaly but because predictable words in context are easier to access from memory. Supporting context allows pre-activation of relevant lexical or conceptual features, making lexical access less effortful²⁰. The lexical view does not imply that N400 amplitude variation in sentences is directly related to the degree of lexical association between words: even in the absence of such associations, the interpretation of the context as a whole has been shown to lead to remarkably specific lexical predictions^{27–31}. The key point is that, although prior semantic composition provided by the sentential or discourse context may give rise to the prediction, the process that underlies the N400 effect is itself non-combinatorial.

This hypothesis implies that any factor that facilitates lexical access should reduce the N400 amplitude, a prediction that is largely borne out in the literature. Words with a higher frequency of occurrence result in smaller N400 responses than lower-frequency words^{32,33}, as do repeated words¹¹. Word-like non-words, which are associated with long reaction times in lexical decision tasks, often elicit larger N400 responses than words^{34–36}. Similarly, although two different mechanisms are thought to underlie semantic priming when different prime–target intervals are used (see below), both lead to an equivalent N400 response reduction, suggesting that the N400 effect is associated with any priming mechanism that increases the activation of a lexical target^{37–40}. Finally, in contrast to the early findings, recent work

Semantic structure

The mental representation of how the meanings of individual words or concepts are combined to yield the meaning of entire phrases or sentences.

Syntactic structure

The mental representation of how the words and phrases within a sentence are organized to form a hierarchically nested structure.

Discourse structure

The mental representation of the information in a conversation or speech act, specifying which information is common knowledge between the speakers, which events or individuals are the current topic of discussion and what are the speakers' communicative goals.

Pseudowords

Auditory or visual strings that sound or look like words but are not actually words (for example, 'blick' but not 'lbikc').

suggests that masked semantic priming can elicit an N400 effect when the interval is short enough^{41,42}.

Anatomical framework for semantic processing

The studies described above have been insufficient to resolve the functional interpretation of the N400 effect, because the contextual factors that ease lexical access could also facilitate semantic integration. We suggest that an emerging neuroanatomical model of semantic processing, anchored in psycholinguistically motivated mechanisms, can break the impasse. By taking into consideration the anatomical regions that are specialized for different aspects of semantic processing, we can use evidence about the localization of the N400 effect to determine what underlying neurocognitive operations this ubiquitous response pattern reflects.

Semantic processing of linguistic material involves the activation and selection of candidate lexical representations and the integration of the semantics of the selected representation with the context that has been constructed on the basis of the previous words. Functional MRI (fMRI), intracranial and neuropsychological studies have implicated three main regions in these computations: the left posterior temporal cortex, the left anterior temporal cortex and the left inferior frontal cortex.

Posterior temporal cortex. The best candidate for the storage of lexical representations is the region that encompasses the left mid-posterior middle temporal gyrus (MTG) and the neighbouring superior temporal sulcus (STS) and inferior temporal cortex (IT)^{43–47}. The left STS and the MTG show fMRI repetition priming (reduced blood-oxygen-level-dependent (BOLD) activity on the second presentation) for auditorily presented words but not pseudowords⁴⁸; this priming is not observed when the task is non-lexical (that is, it is not observed for phonological or first-letter/last-letter alphabetization tasks)⁴⁹. fMRI studies using semantic tasks, such as tasks that require the semantic categorization of words or that require judgments on words' semantic properties, consistently show activity in this region^{50–54}, and studies using distorted speech stimuli find that activity in the MTG and/or the IT increases as a function of intelligibility^{55,56}. Increased activity in the MTG is also observed when the number of words processed per trial is increased⁵⁷. Studies on patients with aphasia show that those with lesions in posterior-temporal areas have difficulty performing semantic tasks that require access to lexical representations^{58,59}. In a study of 64 patients, the MTG was the only region in which lesions led to significantly lower performance on even the simplest sentences⁶⁰. With respect to language production, a meta-analysis of 82 imaging studies found that the left MTG was the only area that was reliably activated for tasks that required lexical selection⁶¹.

These data support the hypothesis that the posterior middle temporal cortex — the MTG and neighbouring parts of the IT and STS — is involved in long-term storage of lexical representations. Which aspects of lexical representations are stored here is unknown. One

possibility is that this region stores not semantic information, but rather lexical representations that interface with a semantic network that is distributed across brain regions⁴⁶: activation in this region in response to tasks involving pictures would thus involve implicit lexical access⁶². However, it is also possible that this area stores the conceptual features that are associated with lexical representations.

The evidence that we have just reviewed suggests that storage of lexico-semantic information is specific to the middle part of the posterior temporal cortex. More ventral parts of the IT are associated with the representation of non-linguistic visual object features⁶³. The posterior superior temporal gyrus (STG) has sometimes been associated with semantic processing, but most evidence suggests that its role is limited to early (auditory) stages of the sound-to-meaning transformation⁶⁴, consistent with early models such as Wernicke's⁶⁵. Imaging studies typically show posterior STG activation for speech and other spectrotemporally complex stimuli regardless of semantic content⁶⁶. Although several fMRI studies show intelligibility effects in the posterior STG as well as in the MTG and IT^{55,67}, it has been suggested that these effects may be driven by top-down processing^{68,69}.

Anterior temporal cortex. Whereas posterior middle temporal areas have been implicated in lexical storage, the anterior temporal cortex seems to support basic combinatorial operations that underlie sentence processing. The anterior STS and MTG and the temporal pole show significant activation during sentence processing in comparison with non-meaningful baselines^{70–74} or lexical-level baselines^{75–81}. This activation seems not to be due to more general aspects of processing meaningful sequential auditory events^{79,82}. Selective damage to the left anterior superior temporal cortex is associated with comprehension impairment for most sentence types⁶⁰. This area may be involved in syntactic or thematic combinatorial operations, as it shows reduced activation in contexts that elicit syntactic priming⁷³. Furthermore, it is activated to a greater extent by sentences than by word lists, even when the sentences or lists contain pseudowords^{77,80}. These results suggest that the anterior temporal cortex supports aspects of elementary combinatorial processing of language, although whether this includes semantic processing is far from clear.

Anterior temporal regions have also been implicated in lexical-level processing on the basis of semantic dementia (SD), a disorder characterized by bilateral anterior temporal atrophy. Patients with SD show deficits in object-naming tasks and single-word comprehension, suggesting that they have damage to lexical storage areas. However, recent work shows that the atrophy that is associated with SD extends to other parts of the temporal lobe^{83–86}. Furthermore, patients with SD show reduced posterior IT activation during semantic tasks⁸⁷. Therefore, the lexical semantic deficits in SD might reflect reduced functionality of posterior middle temporal areas, due to atrophy or to loss of connectivity.

Aphasia

A language impairment that is acquired as a result of stroke or other brain injury.

Syntactic priming

The tendency in language production to formulate sentences with recently used syntactic constructions. For example, when one speaker in a conversation uses a passive construction, other speakers become more likely to use passives.

Angular gyrus. The angular gyrus (AG) may also play a part in integrating semantic information into context. Lesions here are associated with difficulty in processing complex sentences⁶⁰, and imaging studies demonstrate greater AG activity in response to words than non-words and in response to semantically congruent sentences than semantically related word lists or syntactically well-formed but meaningless sentences^{88–93}. Increased AG activity is also found for mismatches between visually presented words or pictures and environmental sounds, suggesting that it may be involved in integrating semantic information from both linguistic and non-linguistic sources⁹⁴.

Inferior frontal cortex. Finally, several areas of the left inferior frontal cortex have reliably been associated with semantic processing. Both dorsal and ventral areas show activation on at least some semantic tasks. Many authors have argued that the anterior ventral inferior frontal gyrus (IFG) is particularly important for semantic processing^{4,89,95–100}, and several studies have shown different activation patterns in the anterior and posterior parts of the IFG, suggesting a separation of function in these two regions^{88,101–103}. Recent work explained this functional segregation^{57,104} by linking the anterior ventral IFG to controlled semantic retrieval and the mid-posterior IFG to selection processes more generally^{105,106}. Studies of semantic ambiguity and priming find that conditions that increase selection difficulty drive increased activity in the posterior IFG, whereas conditions that facilitate retrieval lead to decreased activity in the anterior IFG^{54,107}. In addition to the specific processes of selection and retrieval, the IFG has been linked to the integration of linguistic meaning with world knowledge^{108,109}. However, because the IFG does not show stronger activity for sentences than word lists^{88,92,93}, it is less likely to be involved in combining individual word meanings to compute the semantics of a sentence.

The proposed structural and functional connectivity between these regions during comprehension is presented in FIG. 2. After the stimulus is broken down into phonemic or orthographic primitives (phonological features or letters) in modality-specific regions, these activate matching lexico-semantic representations in the posterior MTG. The anterior inferior frontal cortex drives controlled retrieval of these representations based on context, and the posterior inferior frontal cortex drives selection when multiple representations are highly activated. Although less is known about the neural substrate of semantic and syntactic integration of the word with the previous context, current evidence suggests that the anterior temporal cortex and the AG may mediate these processes, whereas inferior frontal areas may be involved in relating the resulting compositional meaning to stored knowledge about the world. With each new input word, the integrated semantic representation is updated and can then inform subsequent prediction and selection processes that are subserved by the IFG.

This model leads to predictions of the loci of different aspects of word recognition in context, and in particular helps to clarify the functional interpretation

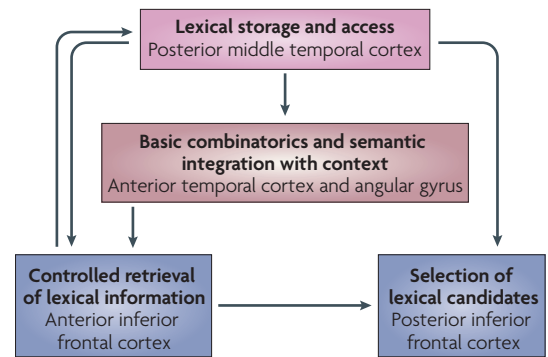


Figure 2 | Schematic model for semantic processing. The components of the model are based on imaging and patient data from a variety of language-comprehension and language-production paradigms. Posterior middle temporal cortical areas (the posterior middle temporal gyrus and perhaps neighbouring parts of the inferior temporal cortex and superior temporal sulcus) mediate the long-term storage of and access to information associated with lexical representations. This 'lexical' information serves as input to higher-order semantic processes. The anterior temporal cortex and angular gyrus have been suggested to support the integration of lexical input into the larger units under construction, such as the syntactic structure, the propositional semantics and the discourse model. The inferior frontal cortex is involved in controlled selection and retrieval of lexical representations. The arrows represent proposed functional connections between areas but carry no implications of known anatomical connectivity; the figure provides only a schematic outline of the proposed information flow. The role of the posterior middle temporal cortex in the storage of lexical information and the role of the inferior frontal cortex in the higher-order processes of selection and controlled retrieval of lexical information are fairly uncontroversial. On the other hand, the areas that underlie the combination and integration of lexical representations are less understood, and the proposed roles of the anterior temporal cortex and the angular gyrus in these processes require further confirmation, as does the contribution of the inferior frontal cortex.

of the N400 effect (TABLE 1). Any parts of the effect that reflect semantic integration or selection/retrieval processes should localize to the anterior temporal, the left inferior parietal and the inferior frontal cortices, whereas any parts of the effect that reflect lexical access processes should localize to the posterior middle temporal cortex. Fortunately, a number of studies have investigated the anatomical origin of the N400 effect.

Localizing the N400 effect

ERP studies. The context-dependent N400 effect in ERP tends to have a centroparietal scalp distribution, with a small but consistent bias to the right side of the head when visual presentation is used¹¹⁰. However, ERP studies with split-brain patients support a left-hemisphere generator for the N400 effect: only sentence completions presented to the 'linguistic' (left) hemisphere elicited N400 effects¹¹¹. Given the strong left-lateralization for language observed elsewhere, the centre-right scalp

Phoneme

Individual units of speech sound used to store the sounds of words in memory.

Split brain

A brain in which the two hemispheres have been separated by severing the commissures that connected them.

Table 1 | Localization in studies of semantic context

Region	Proposed function	Localization of N400 effect predicted by the lexical access account of N400?	Localization of N400 effect predicted by the integration account of N400?	Evidence from localization techniques
Posterior temporal cortex	Storage and access of lexical information	Yes	No	Both short- and long-SOA semantic priming in fMRI ⁵⁴ Semantic priming and semantic anomaly in MEG (~250–500 ms) ^{142,145,147} Semantic anomaly in EROS (~200–400 ms) ¹⁷⁷
Anterior temporal cortex	Combination of lexical representations and/or integration with context	No	Possibly	Semantic priming and semantic anomaly in intracranial studies (medial) ^{156,158} Semantic anomaly in some MEG distributed-source solutions (lateral) ^{147,152}
Inferior frontal cortex	Selection and controlled retrieval of lexical representations	No	Possibly	Long-SOA priming and semantic anomaly in fMRI ⁵⁴ Semantic anomaly in MEG distributed-source solutions ^{147,148,152} Semantic anomaly in EROS (~500 ms or more) ¹⁷⁷
Angular gyrus	Combination of lexical representations and/or integration with context	No	Possibly	No reliable effects observed

This table provides a summary of evidence from studies using localization techniques to examine contextual effects in two standard paradigms that are known to generate an N400 amplitude effect, semantic priming and semantic anomaly. Contextual effects are observed in at least a subset of cases for three areas that have been proposed to have key roles in semantic processing: the posterior temporal, anterior temporal and inferior frontal cortices. Selected references to each set of findings are included. EROS, event-related optical signal; fMRI, functional MRI; MEG, magnetoencephalography; SOA, stimulus-onset asynchrony.

distribution of the N400 effect has been interpreted as ‘paradoxical lateralization’, in which a left-hemisphere generator affects right-hemisphere electrodes owing to fissural morphology and conductance properties^{7,9,112}. Localization from ERP data has occasionally been attempted for the N400 effect^{113–115}, but results have been inconsistent.

Studies of patients with various forms of brain lesion can inform us about the generators of the N400 response by showing that brain damage to particular regions alters the N400 effect. However, the existing data provide limited evidence. The effects of semantic congruity on the N400 response are relatively preserved in patients with amnesia and Alzheimer’s disease^{116–118}, but this result is difficult to interpret because the full extent of the areas that are affected by these disorders is unclear. Similarly, studies of patients with aphasia show that poor language comprehension is associated with a reduced N400 effect for priming and semantic anomaly, but the areas of damage in these patients are often unknown, and patients with Broca’s aphasia and Wernicke’s aphasia can show robust N400 effects^{119–121}. Of studies with smaller sample sizes, one showed N400 congruity effects in three patients with left frontal lesions (although these effects were attenuated)¹²², whereas another found no N400 congruity effect in a patient with a left temporal lesion¹²³. Some further evidence points to temporal involvement: patients with left temporal lobe epilepsy show no N400 congruity effect, in contrast to patients with right temporal lobe epilepsy¹²⁴. In general, however, small sample sizes and heterogeneous aetiologies make it difficult to associate

damage to particular regions with the presence or absence of N400 effects in existing patient studies.

fMRI studies. Previous reviews on the localization of the N400 effect have de-emphasized fMRI evidence, owing to concerns about the differences between fMRI and ERP techniques⁹. The fMRI signal is much delayed relative to ERPs, does not reflect properties such as phase coherence that may contribute to ERP amplitude, and may have a lower signal-to-noise ratio in some cortical areas. These factors also constrain experimental designs. However, we believe that the fMRI evidence from N400 paradigms is both informative and systematic. The spatial accuracy and wide availability of fMRI has led to a wealth of studies using the same contextual manipulations that are used to elicit the N400 effect, allowing us to identify links between specific neuroanatomical regions and components of the model of semantic processing outlined above.

TABLE 2 and FIG. 3 summarize the results of nine studies that compared fMRI signals in response to semantically related and unrelated word pairs — the semantic priming paradigm. The parameters used differ in modality, type of semantic relation and, crucially, stimulus-onset asynchrony (SOA). Psycholinguists have distinguished two kinds of priming¹²⁵: automatic (in which activation automatically spreads through a network of representations that are semantically related to the prime) and strategic (in which the prime is used to generate expectancies for the target or to inform other heuristics for responding to the task quickly). Automatically spreading activation is argued to dominate at short SOAs, whereas strategic processes

Phase coherence

The degree to which two oscillating signals (for example, as measured with electrodes from the scalp) are synchronized.

Stimulus-onset asynchrony (SOA). The time between the onsets of sequentially presented stimuli.

are thought to dominate at longer SOAs^{126,127}. However, N400 effects of similar size are seen at both short and long SOAs in ERP studies^{37–40,128,129} (FIG. 4).

Two patterns are evident across the fMRI priming studies. First, left inferior frontal effects are strongly dependent on the SOA: only priming at long SOAs (>600 ms) affected left IFG activity. In some cases this priming effect appeared in both the anterior and the posterior left IFG, in others only part of the left IFG showed the effect. Importantly, the anterior and posterior left IFG priming effects seem to have separate underlying causes: the posterior left IFG effect was shown to be due to a reduction in activity in the semantically related condition (relative to a neutral baseline), whereas the anterior left IFG effect was shown to be due to an increase in activity in the semantically unrelated condition (relative to the neutral baseline)⁵⁴. Second, the only area with activity that, like the N400 response, consistently shows effects of priming across different SOA values and modalities is the MTG. These patterns are confirmed when primes are presented at both short and long SOAs in the same experiment⁵⁴ (FIG. 4).

The model described above predicts these patterns. For long SOAs, the prime word is fully processed and entered in the current context, making available top-down predictions that can either facilitate the controlled retrieval process that is initiated by the anterior left IFG in related pairs¹⁹³ or increase the burden on the selection process that is initiated by the posterior left IFG in unrelated pairs. Thus, as predicted by the model, in many cases there is no distinction between the effects of priming in the anterior and the posterior left IFG.

It is not clear why several studies showed activity in only one of these areas; however, as this variation was not obviously correlated with particular materials or task demands, it may simply reflect differences in the way that the data were reported in the different studies. The absence of frontal effects in short-SOA studies reflects there being insufficient time for the prime to be processed and entered in the current context, so that the prime cannot influence frontal processes of selection and controlled retrieval based on contextual information. At long and short SOAs alike, however, activation of the correct lexical candidate is made easier, either by top-down predictions in the case of long SOAs or by spreading activation in the case of short SOAs; thus, the model predicts — and the data confirm — that the MTG will show priming effects in both cases.

Some studies implicated a larger part of the posterior temporal cortex (including the STS and the superior IT) in the storage of lexical information. However, these areas did not show up consistently in the fMRI semantic-priming paradigms shown in TABLE 2. These data show that activation in the IT and the STG is sometimes observed but is dependent on specific design parameters of the priming studies (a short SOA for the IT and auditory presentation for the STG), suggesting that their absence in other conditions is not simply a result of spatial smoothing in the fMRI analysis.

The fact that the MTG is the only region with activity that is affected by priming at long and short SOAs provides strong evidence that this area is involved in generating the N400 effect, and thus that the N400 priming effect reflects lexical access. Furthermore, priming

Table 2 | **Functional MRI studies of semantic priming**

Refs	Modality	Task	SOA	IFG			IT	MTG	STG	TP	AG
				BA47	BA45	BA44	BA37	BA21	BA22	BA38	BA39
<i>Short-SOA studies</i>											
177	V	Lexical decision	33					✓			
54*	V	Lexical decision	150				✓	✓			
128*	V	Lexical decision	200							✓	
54*	V	Lexical decision	250				✓	✓			
178*	V	Naming target	250				✓				
<i>Long-SOA studies</i>											
131*	V	Lexical decision	600	✓	✓						
92	A	Lexical decision	600					✓	✓		
179	A	Lexical decision	650		✓	✓				✓	
180	A	Lexical decision	750		✓			✓	✓		
181	V	Relatedness	800	✓	✓			✓			
54*	V	Lexical decision	1,000	✓	✓	✓		✓			
54*	V	Lexical decision	1,000	✓	✓	✓		✓			
128*	V	Lexical decision	1,000							✓	

Significant effects for whole-head contrasts of primed and unprimed targets. Effects in right-hemisphere regions were relatively few and inconsistent across studies, and therefore only left-hemisphere effects are reported here. Effects in the temporal, the inferior frontal and the inferior parietal cortices are reported; no other regions showed consistent effects across studies. Modality of presentation (auditory (A) or visual (V)), task and stimulus-onset asynchrony (SOA) (in milliseconds) are indicated for each contrast. AG, angular gyrus; BA, Brodmann's area; IFG, inferior frontal gyrus; IT, inferior temporal cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus; TP, temporal pole. *Studies that reported contrasts from multiple experiments.

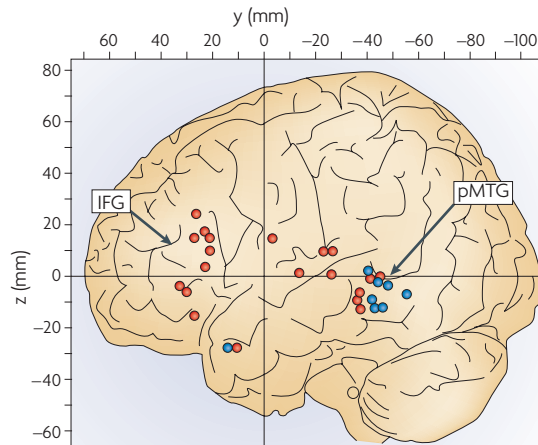


Figure 3 | A visual summary of the results of semantic-priming manipulations in functional MRI. Approximate locations of centres of significant activation in the left inferior frontal and temporal cortices (for references see TABLE 1). These studies differed in the length of the interval between the onset of the prime and the onset of the target, usually referred to as the stimulus-onset asynchrony (SOA). In the behavioural literature, short SOAs are associated with fast, automatic priming; long SOAs are associated with strategic priming^{127,128}. Activation in short-SOA studies (<250 ms) is shown in blue; activation in long-SOA studies (>600 ms) is shown in red. Both short- and long-SOA studies found posterior middle temporal effects (mainly in the middle temporal gyrus (MTG), with additional superior temporal effects in auditory studies), but only long-SOA studies showed inferior frontal effects. IFG, inferior frontal gyrus; pMTG, posterior MTG. Figure modified, with permission, from REF. 176 © (2006) Academic Press.

changes activity levels in the same direction in both fMRI and ERP studies^{54,130}: the primed condition elicits reduced activity relative to a neutral condition. Thus, the directionality of the N400 effect is consistent with the directionality of the MTG effect.

fMRI results for sentence-level studies are less consistent. TABLE 3 summarizes the results of 15 studies that contrasted activity in response to sentences with normal and semantically implausible or unexpected endings. The only region in which activity was consistently affected by contextual semantic fit was the left inferior frontal cortex. These effects were seen in both anterior and posterior inferior frontal areas, although this differed across studies. Only six cases showed a significant effect in left temporal regions, and the location of these effects was highly variable. Note that in sentential contexts the SOA is not a relevant factor, because predictive information accumulates gradually rather than being made available at a single point.

Previous authors have attributed the effects of sentential context on left IFG activity to strategic, task-related processes rather than mechanisms that are normally engaged in language processing⁹. However, left IFG effects were robust across diverse tasks, and were found even in passive-reading paradigms. The model described in FIG. 2 predicts these effects. According to the model,

the left IFG underlies normal processes of controlled retrieval and selection of lexical representations. When a critical word is predicted based on prior context, lexical retrieval (performed by the anterior left IFG) should be easier; when a different word is predicted, or when the context does not support the input, lexical selection (performed by the posterior left IFG) of the correct word should be harder. Thus, the model would not predict any distinction between the effects of congruency on the anterior and posterior left IFG. Again, although some studies report effects in only part of the left IFG, this variation did not obviously correlate with any design parameters.

How are the IFG effects that are observed in fMRI studies manifested in the ERP waveform? One possibility is that the frontal effect in the ERP appears as an increase in the amplitude of the late positivity that follows the N400 response, sometimes called the 'post-N400 positivity' (REFS 9, 131, 132). In many N400 studies, the incongruous condition produces an ERP that not only is more negative at the N400 peak, but also is more positive at the broad positive peak that follows. This effect seems to be greatest in cases in which the anomalous word is semantically or phonologically related to the expected ending^{20, 133–137}; such cases might require more effortful selection or inhibition from the posterior IFG.

More surprising is the inconsistency of the effects of sentential context in the temporal cortex. This is problematic, given that the MTG is the only region that follows the N400 pattern in showing semantic priming effects across SOAs. We suggest that MTG effects have failed to show up in existing fMRI results for several reasons. First, the temporal insensitivity of fMRI means that it is most effective at identifying distinctive activation within an interval of a few seconds. Modulation of lexical access processes in priming contexts is fairly distinct, as the prior context consists of only a single word; however, modulation of lexical access due to a predictive sentence context may not stand out against the many and varied lexical-access events that occur over the course of any sentence. Distinguishing lexical-access effects from this background may require targeted fMRI designs. Second, the manipulations of sentential context that were used in most fMRI studies differed from those used in most ERP N400 studies, in which the sentence contexts were designed to strongly predict a particular ending, such that the conditions differed in both semantic congruity and expectancy. Conditions that differ only in semantic congruity show smaller differences in N400 amplitude^{19,136}, consistent with the view that the 'semantic anomaly' N400 effect is driven not by the anomaly but by predictive pre-activation in the congruent condition. In many of the fMRI studies, materials were designed to be anomalous but not necessarily predictive, and thus they may have elicited a weaker context effect.

The best opportunity to identify N400 generators should arise in fMRI experiments that explicitly manipulate expectation instead of, or in addition to, congruity. Indeed, an fMRI contrast of non-anomalous endings to highly predictable contexts showed a main effect of expectancy in the MTG¹³⁸, and another fMRI study showed parametric modulation of the MTG and

IT with expectancy of sentence ending¹³⁹. Still another study created predictable contexts for congruent and anomalous sentences and showed both a robust N400 effect and significant fMRI activation in the STG and STS¹⁴⁰. These results suggest that the larger part of the classic N400 effect in semantic priming and anomaly is a consequence of facilitation of lexical access due to expectation, and not a consequence of the anomaly *per se*¹⁰⁸.

Neither the semantic-priming nor the semantic-anomaly studies showed consistent effects in the anterior temporal cortex (anterior STG or temporal pole). This follows from the model, which predicts anterior temporal effects when sentences are directly contrasted with words but not when conditions differ only on the ease of accessing lexical representations — as the lexical-access account of the N400 response proposes for both the priming and anomaly manipulations. However, the anterior temporal cortex is known to be susceptible to fMRI signal artefacts, particularly in the medial region that has been implicated in N400 response generation by the intracranial studies discussed below¹⁴¹ (this medial region is distinct from the anterior STG region that shows sentence versus word effects). Thus, we cannot rule out the possibility that this artefact masks real effects of semantic priming and anomaly in the anterior temporal cortex.

Magnetoencephalography studies. Magnetoencephalography (MEG) studies that examine the N400 effect use both equivalent current dipole (ECD) models and distributed-source models to estimate its source. Although achieving precise source estimates is difficult, MEG allows robust discrimination between activity generated in the left versus the right hemisphere and anterior versus posterior cortical areas over time, and can thus provide supporting evidence for the time course of activity in areas identified with fMRI.

Studies of semantic priming and semantic anomaly that use ECD source analysis uniformly report a response that localizes to the left mid-posterior MTG, STS and STG, that has an onset of ~250 ms in auditory presentation^{142,143} and ~300–350 ms in visual presentation^{144–149}, and that has a peak latency of 410–450 ms. Recent MEG studies have estimated the source of the semantic anomaly effect using a distributed-source model based on the cortical surface^{150,151}. Early effects (at 250–500 ms) were observed in the left planum temporale and left MTG and IT¹⁴⁷. Additional areas — the left anterior temporal and inferior frontal cortex and the right orbital and anterior temporal cortex — were implicated in the later part of the anomaly response, which may reflect either the latter part of the N400 effect or the post-N400 positivity. However, other studies using distributed-source models have found somewhat different results^{148,151}, so clarification is needed. Nevertheless, all methods of MEG source analysis have converged on the finding that the left mid-posterior temporal cortex is one source of the N400 effect. Furthermore, a recent study using simultaneous recordings of ERP and the event-related optical signal (EROS)

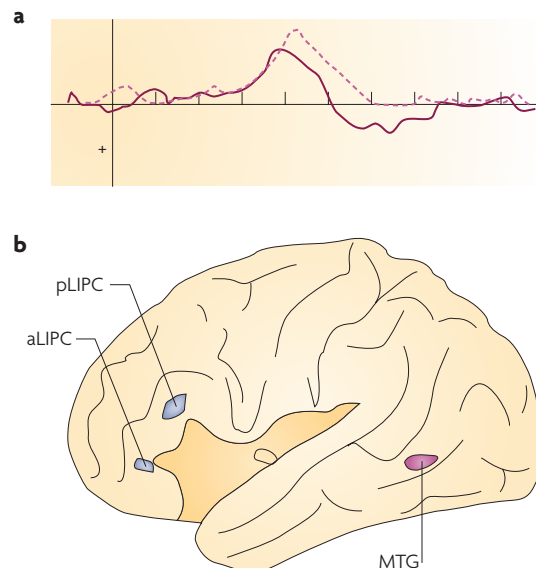


Figure 4 | Semantic priming at short and long SOAs. A critical parameter in semantic-priming experiments is the length of the stimulus-onset asynchrony (SOA): the interval between the onset of the prime and the onset of the target. **a** | Event-related potential (ERP) difference waves (the waveforms that are obtained by subtracting the related from the unrelated condition) for semantic priming with 200 ms SOA (dotted line) and 800 ms SOA (solid line). An N400 effect of similar amplitude is observed at both SOAs. **b** | Functional MRI semantic-priming effects at 250 ms SOA and 1,000 ms SOA. The middle temporal gyrus (MTG) cluster showed priming effects at both SOAs, whereas the left inferior parietal cortex (LIPC) clusters (one anterior (a) and one posterior (p)) showed priming effects only for the 1,000 ms SOA condition. Part **a** reproduced, with permission, from REF. 37 © (1995) Cambridge University Press. Part **b** reproduced, with permission, from REF. 54 © (2006) Society for Neuroscience.

corroborated the MEG source estimates: left-hemisphere responses to semantically anomalous sentence endings were observed in the mid-posterior STS and MTG at 200–400 ms, with contributions from anterior temporal and inferior frontal areas only after 500 ms¹⁵².

Intracranial recordings. Further evidence on the source of scalp-recorded N400 effects derives from intracranial recordings collected from surface or depth electrodes on pre-operative epilepsy-surgery candidates. The drawback of this method is that findings are limited to the areas that are plausible epileptogenic zones, often the anterior medial temporal lobe (AMTL) and inferior temporal areas.

Many studies recording from anterior medial temporal locations have found a 400–450 ms latency evoked response to visually presented words that shares many properties with the N400 response^{153–157}. The amplitude of this AMTL response has been shown to correlate with the scalp-recorded N400 response in semantic-priming and semantic-anomaly paradigms^{156,158}. However, the restricted anatomical coverage of this technique has limited information about other regions. Intracranial recordings have demonstrated

Equivalent current dipole (ECD) models

Estimates of the focal source of neuronal activation derived from multi-sensor data obtained by electroencephalography or magnetoencephalography. The activation is modelled as a point source with a position, direction and intensity.

Distributed-source models

Estimates of the neuronal sources that underlie the brain activity that can be represented with magnetoencephalography or electroencephalography multi-channel data. Activity is not assumed to be focal, permitting a spatially distributed and perhaps more realistic visualization.

Table 3 | **Functional MRI studies of semantic anomaly**

Refs	Modality	Task	IFG			FFG	IT	MTG	STG	TP	AG
			BA47	BA45	BA44	BA36	BA37	BA21	BA22	BA38	BA39
182	A	Animacy			✓				✓		
183	A	Accuracy judgment							✓		
140	V	Accuracy judgment	✓	✓	✓			✓	✓		
184	V	Accuracy judgment	✓	✓		✓	✓			✓	
185	V	Accuracy judgment	✓			✓					
186	A	Accuracy judgment	✓								
187*	A	Accuracy judgment	✓								
187*	A	Accuracy judgment		✓							
187*	A	Accuracy judgment	✓	✓				✓			
188	V	Accuracy judgment			✓						
189	V	Accuracy judgment	✓				✓				✓
190	V	Accuracy judgment									✓
191	A	Lexical decision		✓	✓						
138	V	Lexical decision	✓								
108	V	None	✓	✓							
192	V	None			✓						
139 [†]	V	None		✓							

Significant effects for whole-head contrasts of anomalous and congruous sentences in left-hemisphere language areas. Effects in right-hemisphere regions were relatively few and inconsistent across studies, and therefore only left-hemisphere effects are reported here. Effects in the temporal, the inferior frontal and the inferior parietal cortices are reported; no other regions showed consistent effects across studies. The modality of presentation (auditory (A) or visual (V)) and task are indicated for each contrast. AG, angular gyrus; BA, Brodmann's area; FFG, fusiform gyrus; IFG, inferior frontal gyrus; IT, inferior temporal cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus; TP, temporal pole. *Studies that reported contrasts from multiple experiments. [†]This study used verb phrases (for example, "broke rules" and "ate suitcases") rather than full sentences.

an N400 evoked response in areas including the anterior IT¹⁵⁶, the prefrontal and orbitofrontal cortex and the posterior lateral STG and MTG^{154,155,157}, and repetition-priming effects have been demonstrated at MTG sites¹⁵⁷, but contextual manipulations have not been tested in these areas.

The intracranial recordings provide evidence that activity in the AMTL correlates with the scalp-recorded N400 response on several measures, raising the possibility that this area is an additional N400 generator. However, a non-generator region could also reflect N400 patterns if its function were partially contingent on the factors that drive MTG activity. Indeed, intracranial recordings from the AMTL demonstrate a response opposite to the scalp-recorded N400 response to pronounceable non-words¹⁵⁶, which is typically larger than the N400 response to real words^{34–36}. Unfortunately, fMRI data are inconclusive with respect to the contributions of this area to the N400 effect, as measurements in anterior temporal areas often suffer from artefact-induced signal loss or lack of coverage.

Summary and future directions

Many existing findings on the anatomical source of N400 effects have had a limited impact on the functional interpretation of these effects. We have argued that a model of the neuroanatomy of semantic processing derived from the imaging and patient literature leads to a clearer understanding of the contextual-processing

mechanisms that underlie the N400 effect. Current models predict that contextually facilitated accessing of stored lexical and/or conceptual representations should be reflected in the posterior middle temporal cortex, whereas ease or difficulty of selecting and integrating stored representations with the prior context should be reflected in the anterior temporal, inferior parietal and inferior frontal regions. Our review and analysis of fMRI and MEG studies (TABLE 1) provides strong evidence that the N400 effect reflects facilitated access: the posterior middle temporal cortex is the only area to show effects of semantic priming in fMRI across all the conditions that typically show an N400 effect, and MEG studies of semantic priming and anomaly localize the effects to the same area. This evidence allows us to rule out a purely integrative account of the N400 effect. However, integration mechanisms still play an important, albeit indirect, part in the processes that lead to the lexical facilitation that is reflected in the N400 effect, in that it is the propositional structure and discourse model constructed on the basis of prior material that provide the predictions that facilitate access.

These data strongly suggest that at least some substantial part of the N400 effect reflects facilitated lexical access, and thus that the N400 effect cannot be attributed only to post-access processes. These data do not provide any conclusive evidence to support the integration account of the N400 effect, but they also do not rule out the possibility that the effect reflects a combination of

inputs from multiple semantic regions over its duration of several hundred milliseconds, some or all of which may contribute to the effect in a particular paradigm^{134,147,159}. In addition to the posterior middle temporal effects, a subset of studies also show effects in inferior frontal regions, probably reflecting differences in ease of selection or retrieval or — in some models — integration with world knowledge. These effects may be reflected in a subsequent late positivity, but they may also contribute to the N400 effect. The anterior temporal cortex may also contribute to the scalp-recorded N400 but fail to be represented in fMRI data for method-specific reasons. Although we cannot discriminate between these possibilities yet, the framework described here generates specific anatomical predictions that can be tested more systematically, with a focus on examining the convergence and divergence of particular aspects of the signal in different methodologies across psycholinguistic manipulations.

The data reviewed here support the framework for semantic processing that is presented in FIG. 5. Amodal lexical representations, linked to distributed semantic representations throughout the cortex, are stored and activated in the posterior middle temporal cortex and in parts of the neighbouring STS and IT. These representations are more easily accessed in predictive or priming contexts, leading to a reduction of activation that is reflected in the N400 effect and in corresponding BOLD signal reductions. During sentence processing, these lexical representations are accessed by the anterior temporal cortex and angular gyrus, which integrate the current input into the semantic and syntactic context that is under construction. The anterior inferior frontal cortex mediates top-down controlled semantic retrieval of lexical representations, which is partially based on the updated representation of the global semantic structure that is provided by integration areas. This top-down retrieval facilitates lexical access, indirectly contributing to a reduction in MTG activity. The posterior inferior frontal cortex mediates selection among highly activated lexical representations, partially based on the current global semantic representation.

Most of the contextual manipulations focused on in the second part of this Review allowed pre-activation of lexical information, and thus highlighted the role of the posterior middle temporal cortex in the processing of words in context. Paradigms that selectively manipulate integrative processes at different levels of representation (that is, syntactic, semantic and discourse levels) will be needed to provide more evidence for the contributions of the combinatorial and control regions proposed by the model, which are less well established.

It must be acknowledged that the concepts that underlie this model remain poorly understood. First, we do not have even a rudimentary understanding of the neuronal architecture of the middle temporal gyrus, not to speak of its cognitive function. Although we have reviewed diverse evidence for the MTG's involvement in the storage and access of lexical representations, it is not clear whether the stored information involves word-specific 'lemmas' (non-linguistic semantic or

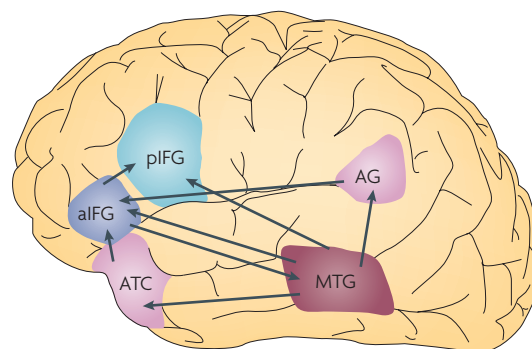


Figure 5 | A functional neuroanatomic model for semantic processing of words in context. Lexical representations are stored and activated in the middle temporal gyrus (MTG) and in the nearby superior temporal sulcus and inferior temporal cortex, and are accessed by other parts of the semantic network. The anterior temporal cortex (ATC) and angular gyrus (AG) are involved in integrating incoming information into current contextual and syntactic representations. The anterior inferior frontal gyrus (aIFG) mediates controlled retrieval of lexical representations based on top-down information, and the posterior IFG (pIFG) mediates selection between highly activated candidate representations.

conceptual features). In support of this possibility, several ERP studies show a contextual priming effect similar to the N400 effect for pictures^{15–17,160}, videos^{161,162} and environmental sounds^{112,163,164}, although the scalp distribution of these effects is slightly different from the standard N400 effect for words. A focused programme of research investigating the response properties of MTG neurons and/or ensembles will be required to elucidate the MTG's contribution to lexical representation and processing.

Second, although our model proposes that several regions are likely to be involved in semantic integration, the notion of integration requires specification both at the level of cognitive models and at the level of neuronal mechanisms. For example, psycholinguistic models of the integration of words into larger units, such as sentential and discourse representations^{165–167}, have rarely been linked to neurophysiological findings¹⁰⁹. We have suggested here that integration covers multiple sub-mechanisms: encoding compositional structure, generating expectations, linking input with world knowledge, and controlling communication between different information sources. However, we leave open the specific technical implementation of these mechanisms; it seems plausible that integration at different representational levels will be associated with different neuronal populations.

Finally, the central idea of prediction raises questions regarding the representational levels at which predictions are implemented. The construction of mental models entails broad prior accessing of likely input representations, the construction of sentences within a discourse entails more specific predictions about syntactic and semantic information, and very specific predictions (such as those for particular visual

Mental models

Internal psychological representations of actual or hypothetical situations that can guide perception, action and reasoning.

or auditory features) may be instantiated based on partial representations derived from the input. The computational mechanism by which predictions are implemented is unknown, and various schemes have been proposed^{168–170}. Constructing a complete model of how prediction and integration interact in language processing will require substantial advances in our theoretical understanding of these mechanisms; our schematic model provides a starting point.

With a wave of new research on predictive processing^{2,26,94,171–175}, the field of language processing is now poised to advance beyond the separate study of ‘lower-level’ processes of accessing lexical–semantic representations on the one hand and ‘higher-level’ processes of integration and top-down contextual influence on the other to a consideration of the interaction between such operations. We show that a better understanding

of this interaction across time demands that we distinguish between regions that play a necessary part in the process and regions with activity that is actually affected at the point when the measure is collected. Models that make explicit claims about the regions that are involved across levels and that can be tested against empirical findings across a battery of neuroanatomical and electrophysiological measures will be instrumental in resolving these issues.

Note added in proof

We recently became aware of a relevant recent fMRI study¹⁹³ showing that semantic-priming effects are modulated in location and directionality by the task used. The authors relate this task-dependency to the automatic and strategic priming mechanisms responsible for the SOA effects reviewed here.

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