

Semantic memory retrieval circuit: Role of pre-SMA, caudate, and thalamus

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ABSTRACT

We propose that pre-supplementary motor area (pre-SMA)–thalamic interactions govern processes fundamental to semantic retrieval of an integrated object memory. At the onset of semantic retrieval, pre-SMA initiates electrical interactions between multiple cortical regions associated with semantic memory subsystems encodings as indexed by an increase in theta-band EEG power. This starts between 100–150 ms after stimulus presentation and is sustained throughout the task. We posit that this activity represents initiation of the object memory search, which continues in searching for an object memory. When the correct memory is retrieved, there is a high beta-band EEG power increase, which reflects communication between pre-SMA and thalamus, designates the end of the search process and resultant in object retrieval from multiple semantic memory subsystems. This high beta signal is also detected in cortical regions. This circuit is modulated by the caudate nuclei to facilitate correct and suppress incorrect target memories.

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1. Introduction

Many conceptual and mechanistic models for semantic memory storage and retrieval have been proposed over the years, mostly informed by lesion/deficit observations and functional imaging studies, and less frequently by electrophysiology studies (Caramazza, Hillis, & Rapp, 1990; Caramazza & Shelton, 1998; Gainotti, 2000; Hillis, Rapp, Romani, & Caramazza, 1990; Humphreys & Forde, 2001; Mahon & Caramazza, 2003; Moss, Tyler, & Devlin, 2002; Tyler & Moss, 2001; Warrington & McCarthy, 1987; Warrington & Shallice, 1984). Each of these models has focused on different and important aspects of semantic memory storage and retrieval. Semantic object memory in particular has been a focus of these models given that objects are tractable stimuli for experimental manipulation. Although these models have been refined over the years to better explain the anatomical and neurophysiological basis of semantic object storage and retrieval, they remain incomplete.

Hart, Kraut and colleagues (for a more detailed description see Hart et al., 2007 or Hart & Kraut, 2007; Kraut, Calhoun, Pitcock, Cusick, & Hart, 2003; Kraut, Pitcock, & Hart, 2004) proposed a

model of semantic object memory called the Neural Hybrid Model of Semantic Object Memory (ver. 1.1), which posits multiple semantic memory subsystems that encode object representations in sensorimotor and higher-order cognitive systems (e.g., lexical–semantic, visual, auditory, tactile, etc.). The neural representations in these cortical regions contain both *feature-based* (see Hart & Gordon, 1992; Haxby et al., 2001; Miceli et al., 2001 for further description of featural organization) and *category-based* (Kraut et al., 2006) neural representations for several of these sensorimotor/cognitive domains. The model supports the idea of functional–anatomic organizations for featural representations within modality-specific sensorimotor/cognitive domains that encode for features of either items or groups of items in a category (e.g., visual–perceptual features for animals; Hart & Gordon, 1992; Haxby et al., 2001; Miceli et al., 2001; Sartori & Job, 1988; Sartori, Job, Miozzo, Zago, & Marchiori, 1993) or across groups of items/categories (e.g., manipulability as a feature, detected in the premotor regions for both tools and fruit and vegetables, Kraut, Moo, Segal, & Hart, 2002; threat as a feature in the auditory- and visual semantic subsystems, Calley et al., in press; Kraut et al., 2006). The model also proposes a categorical organization, consistent with multiple accounts, including the domain-specific account.

In our model, these categorical and featural stores can link with each other in a variety of ways (for example, additive, distributed), partly depending on modality of the stores (see Hart & Kraut, 2007 for details). Here, “additive” means when two separate anatomic

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nodes, each encoding for distinct and separate qualities (e.g., in nonverbal sound memory, one region for threatening sounds and another for animal sounds), are both activated when both qualities are associated with an object representation probed by the stimulus; “distributed” as used here means that a given quality is encoded across multiple nodes, with the possibility that each node may be responsive to more than one quality. Semantic ‘links’ that could be mediated by neural activity in these stores include intra-modal as well as multimodal (across multiple sensorimotor or cognitive domains) relationships between semantic entities from different subsystems that subservise semantic memory. An example of an intra-modal interaction is the lexical–semantic association for the meaning of the words “wing” and “bird”, while an example of a multimodal semantic relationship is the association between the visual memory representation of a dog’s tail and the word “dog” (Beauchamp, Lee, Argall, & Martin, 2004; Hart & Gordon, 1992).

The hybrid nature of the model extends from both the functional and anatomic domains consisting of combinations of differing neural architectures (e.g., nodes representing a population of neurons for the implementation of cognitive operations, spatially distributed neural patterns that encode for specific entities, etc.) to account for the dynamic mechanisms of storage, operations upon, and retrieval of semantic object knowledge. Neuronal nodal populations in this model have been imputed to perform a variety of operations including the following ones: (1) processing semantic information or performing semantic operations, (2) integration of input from multiple representational levels (Beauchamp et al., 2004; Hart & Gordon, 1990), (3) access to individual memory encodings that are represented by spatially or spatiotemporally distributed patterns, to name several. Examples of specific operations utilizing semantic representations include category, property, synonym judgments, multimodal integration (Hart et al., 1998; Hillis et al., 2001); selection of semantic knowledge amongst alternative choices (Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997); categorization of animals and artefacts (Perani et al., 1995); and selection of color attribute or location (Mummery, Patterson, Hodges, & Price, 1998). Other semantic processes and regions that form a network of regions engaged in semantic operations continue to be identified (Binder, Desai, Graves, & Conant, 2009).

An important cognitive process in semantic memory is object retrieval. In this review, we delineate interactions between the rostral aspect of dorsomedial Brodmann Area 6 (referred to hereafter as for pre-supplementary motor area), thalamus, and caudate for semantic object retrieval, further specifying the neural underpinnings of this aspect of the Neural Hybrid Model. We have previously posited that retrieval of an integrated object concept in semantic memory involves the co-activation of representations of features and categories that characterize an object, which are then integrated by means of synchronized neural activity modulated by the thalamus (Kraut, Kremen, et al., 2002; Slotnick, Moo, Kraut, Lesser, & Hart, 2002). We will further elaborate on the cognitive constructs mediated by pre-SMA, caudate, and thalamus in this retrieval circuit. We have begun to impute roles to these structures using a variety of investigative techniques in both normal control participants and in patient populations (e.g., schizophrenia, Gulf War Illness, stroke, and dementia) and using several semantic memory tasks (semantic object retrieval tasks, semantic inhibition tasks).

Several findings motivated the proposition of the neural hybrid nature of the model. First, the reports of evidence of both category and feature representations in multiple semantic object memory subsystems implies a mechanism to integrate these dissociable representational units (Hart, Berndt, & Caramazza, 1985; Hart & Gordon, 1992; Sartori & Job, 1988; Warrington & McCarthy, 1987). Lesion deficit studies have also demonstrated that damage to discrete anatomic regions disrupts specific semantic processes,

leaving other processes intact (Demb et al., 1995; Fiez, 1997; Hart & Gordon, 1990; Posner, Petersen, Fox, & Raichle, 1988). This led to the proposal that specific anatomic regions are involved in the mechanism of combining object components into an integrated object memory. As the object components are represented across multiple modalities, the idea emerged that some anatomic regions process semantic properties within a domain (domain-specific) while others are likely engaged in more general cognitive processing (domain-general).

Several semantic-specific and domain-general regions were proposed to be involved in the semantic retrieval process. We hypothesize that the primary regions critical to this process are the pre-SMA, caudate and thalamus with other regions subserving more specific retrieval roles. As the pre-SMA is involved in semantically driven word generation (Crosson et al., 2001), particularly in searching for item members of a particularly category (Crosson et al., 2003), we hypothesized that the pre-SMA is essential in initiating an item search. The caudate has been found in both motor (Picard & Strick, 1996) and cognitive functions (Crosson, Benjamin, & Levy, 2007) to be engaged in enhancing neural activity related to correct choices and suppressing activity related to incorrect ones, including in selecting meanings for words (Copland, Chenery, & Murdoch, 2000, 2001). Importantly, the caudate engagement appears to be dependent upon task/stimulus difficulty, suggesting that it will be variably engaged depending on the complexity of the retrieval task and likely utilized in semantically difficult or complex retrievals (Copland, 2003). The thalamus has been proposed to gate information flow between spatially separated cortical regions (Nadeau & Crosson, 1997) or to modulate activation of mental representations (von Zerssen, Mecklinger, Opitz, & von Cramon, 2001), either of which would be essential in integrating multiple semantic memory subsystems into a cohesive memory. Other plausible regions that may be engaged in semantic retrieval include those associated with multimodal semantic processing – inferior parietal–posterior temporal (Beauchamp et al., 2004; Grossman et al., 2003; Hart & Gordon, 1990), temporal poles (Damasio, 1990), temporo-parietal-occipital (TPO) junction (Mummery et al., 1998), and left lingual–fusiform gyri region (Hart et al., 1998; Perani et al., 1995) – and any or all of these areas may play roles in the elicitation of an integrated memory. In our work we clarified the individual roles played by the pre-SMA, caudate and thalamus in semantic retrieval as well as evidence of how these regions are engaged.

2. Semantic Object Retrieval Task (SORT) and its fMRI, time-dependent beta-band EEG power change, and ERP correlates

The functional–anatomic organization within modality-specific sensorimotor/cognitive domains include perceptual (e.g., visual–perceptual features; Hart & Gordon, 1992; Haxby et al., 2001; Miceli et al., 2001; Sartori & Job, 1988; Sartori et al., 1993), sensorimotor (e.g., manipulability, as encoded in hand-related in premotor regions for both tools and fruit and vegetables; Kraut, Moo, et al., 2002), or emotional features (threat as detected in the nonverbal sound system, Kraut et al., 2006, visual semantic system, Calley et al., *in press*) as well as category level knowledge and other potential subcomponents related to objects. We posited that a unified object representation is retrieved in semantic memory by integrating these anatomically separated, modality-specific representations. This proposal is in contrast to assertions that information flows from each different modality to an amodal semantic system, with these amodal, semantic-specific regions encompassing where an integrated object memory is encoded and retrieved (e.g., temporal pole, Damasio, 1990). To test the validity of our hypothesis, we constructed a task that probes object retrieval from the integration of

two features of the object (semantic object retrieval task – SORT). For example, participants were visually presented the words, ‘desert’ and ‘humps’, and were to push a button if the two words result in the participant thinking of a specific object (in this case ‘camel’). Administration of this task during fMRI showed that successful retrievals compared to nonretrievals elicited differentially greater signal changes in pre-SMA, the caudate nuclei, the thalamic pulvinar nuclei, and ventral temporo-occipital lobes (the “what” visual memory system) (Kraut, Kremen, et al., 2002; Kraut et al., 2003; As-saf et al., 2006).

Pulvinar involvement in this process, with its role in mediating/modulating electrophysiological signals along with its rich connections to posterior language regions and visual association cortices, motivated speculation that synchronizing brain rhythms play a key role in activating an integrated semantic memory (Crosson, 1999). In a patient with implanted thalamic electrodes (Slotnick et al., 2002), we recorded thalamic depth and surface scalp electrical activity as the patient performed the above-described SORT task. We found that during successful object retrievals compared to nonretrievals, there was a spatially specific, phase-locked, high beta (21–34 Hz) EEG power increase at thalamic and occipital scalp electrodes, whose time could not be accurately determined but which appeared to occur late in task performance. We interpreted this thalamo-cortical activity to reflect integrated object retrieval. Medial portions of the pulvinar connect with inferotemporal visual cortex as well as with somatosensory cortex, insula, and amygdalae, where features and other component elements of an object are encoded (Gutierrez, Cola, Seltzer, & Cusick, 2000; Sherman & Guillery, 2002). Given its rich interconnections with those regions, the pulvinar is ideally positioned to synchronize inter-regional neural activity and thus to integrate those semantic elements into an integrated object representation.

Several lines of research have implicated the role of pulvinar in synchronizing inter-regional neural activity. Shipp (2003) proposed that the pulvinar coordinates cortical information processing to different regions by facilitating and sustaining synchronized cortical activity, which has been supported by modeling in simulations (Gollo, Mirasso, & Villa, 2010). The pulvinar’s role in modulating these synchronizing rhythms with cortical regions was experimentally examined in animal models by injecting GABA agonists to the pulvinar, which resulted in decreased strength of thalamo-cortical oscillations as measured by electrophysiological recordings (Shumikhina & Molotchnikoff, 1999). Studies in cats during which local field potentials from the pulvinar and visual cortices were recorded has further demonstrated that when attention is directed to a visual cue, there is an increase in high beta synchrony between the thalamus (pulvinar and LGN) and both primary and secondary visual cortices (see Wrobel, 2000). This was further supported by studies of pigeons visually-attending to target objects. Those investigators showed that the pulvinar nucleus modulates synchronizing rhythms to tectal and extrastriate cortex for target but not distracting stimuli (Marín et al., 2012).

Activation of the caudate nuclei with successful object retrieval is consistent with our proposal that this structure is engaged in complex retrieval tasks to suppress incorrect and enhance correct choices/operations. The caudate’s role in semantic processing has been extensively described by Crosson and colleagues (Crosson et al., 2007) and, while it does not appear that this part of the basal ganglia is directly involved in semantic functions, there are data that indicate the caudate’s involvement in a variety of cognitive operations. Relevant to the retrieval process, the “direct loop” neural circuit that includes the caudate affects cognition by enhancing activity in a cortex–caudate–medial pallidal–thalamus–cortex circuit. Another relevant caudate-related function is mediated by the “indirect loop”: a cortex–caudate–lateral pallidal–subthalamic nucleus–medial pallidal–thalamus–cortex circuit that suppresses

competing or irrelevant cognitive operations, all of which have been proposed to be mediated by posterior caudate connections to the thalamus. Given the apparent roles of these two circuits, we posit that the caudate is involved in semantic retrieval by facilitating thalamo-cortical transmission and thus selection of the correct object (direct loop keeps the correct set of representations activated longer), and by suppressing the retrieval of competing but incorrect objects (indirect loop) by decreasing these thalamo-cortical interactions. In this schema, prolonged neural activity in the cortical representations of the components of the object (features, category assignment, associates, etc.) that optimally fits the search criteria facilitates emergence of and thus retrieval of the correct semantic memory.

We next administered the SORT task to 19 young, normal control adults while we recorded EEG at the scalp and then derived event-related potentials (ERP). A significant difference in the ERP between the retrieval and nonretrieval waveforms (with nonretrievals more negative than retrievals) was detected over the left anterior fronto-temporal regions at about 750 ms, indicating a divergence in processing between object retrievals and nonretrievals. We propose that this ERP divergence occurs when the activated feature representations of the stimuli are correlated with each other in the trials during which an object memory is retrieved (Brier, Maguire, Tillman, Hart, & Kraut, 2008). It should be kept in mind that this rather long 750 ms interval subsumes reading the two words that represent the feature stimuli and determining what each of them means, both of which have to take place before further processing can occur. In a version of this task where feature stimuli are sequentially presented and ERPs recorded from presentation of the second stimulus, preliminary analysis (unpublished results) reveals this same ERP is present between 400–500 ms and thus resembles a more typical N400 associated with semantically unrelated/related stimuli. While this potential exhibited its maximal amplitude over the left anterior fronto-temporal region, it cannot be assumed that the generators of this potential lie immediately subjacent to this location on the scalp, given considerations of the cellular configurations of individual cortical (or even subcortical) generators, and the different ways that potentials from multiple spatially separated generators can summate at the scalp. Thus, amongst the plausible contributors to this ERP are left frontal, rostral left temporal cortical regions, and even other more deeply situated structures (e.g., left inferior temporo-occipital regions).

To further delineate the other temporal and possibly mechanistic markers of semantic object retrieval, we analyzed the temporal properties of the EEG power spectra over the entire scalp from 25 normal subjects who performed the SORT task (Ferree, Brier, Hart, & Kraut, 2009). Starting at approximately 150 ms and extending to until after the button push, we detected an increase in EEG power at about 4 Hz (Fig. 1). This power increase was present in both retrieval and in nonretrieval trials, and while widespread, it was maximal in amplitude over the dorsal frontal lobes and over the

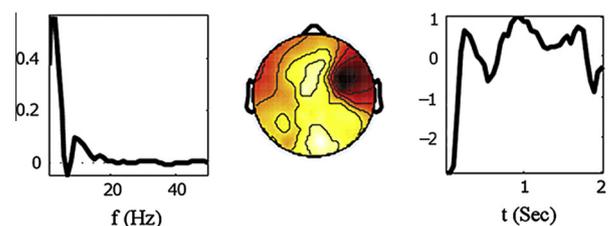


Fig. 1. The three panels above designate the frequency (left), location (middle), and time course (right) of the significant time–frequency changes in the SORT task. This figure shows significant time frequency changes at approximately 4 Hz, maximally located over the dorsomedial midline frontal region and the parietal, posterior temporal, and occipital regions (maximally at the occipital pole), and extending from approximately 100 ms throughout the entire time course of the task.

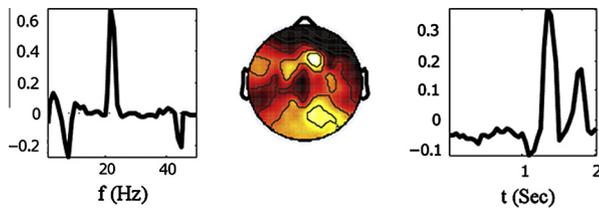


Fig. 2. Significant time–frequency change in the SORT task noted at approximately 25 Hz, maximal over the dorsomedial midline frontal region and the occipital pole, and occurring at approximately 1100 ms for a duration of 100–200 ms.

parieto-occipital regions, bilaterally. Since this was present across all trials, we posit that it reflects the initiation of the semantic object search process and a mechanism through which inter-regional communication is mediated or at least facilitated.

We also detected a significant increase in high beta (21–34 Hz) power at midline frontal electrodes (AF4 and F5) for the retrieval trials as contrasted with nonretrieval trials (Fig. 2). The time courses of the EEG power changes at these two electrodes are nearly identical, suggesting functional coupling between these locations, and occurred at approximately 1100 ms in the time course of the task (mean retrieval RT \sim 1325 ms), again plausibly reflecting intra-frontal lobe communications related to successful completion of the object retrieval process. This 1100 ms midline frontal high beta power change is at roughly the same frequency as the thalamic and occipital electrodes in the patient with depth electrodes (Slotnick et al., 2002), and we propose that it reflects inter-regional signals signifying the resolution of the object search process and retrieval of the integrated object memory.

The dorsomedial frontal high beta EEG power increases recorded at the scalp correspond spatially to the pre-SMA signal changes seen in multiple fMRI semantic object retrieval studies (Kraut, Kremen, et al., 2002; Kraut et al., 2003; Assaf et al., 2006). The thalamic EEG electrode was located in the dorsomedial (DM) thalamic nuclei, but the electrode likely also recorded volume-conducted activity from other thalamic regions. Other fMRI studies provide evidence that multiple thalamic nuclei are active during performance of this task, demonstrating signal changes in both the pulvinar and dorsomedial nuclei (Assaf et al., 2006). Thus, high beta findings in pre-SMA, thalamus, and occipital region in the SORT correspond at least roughly with previously discussed fMRI signal changes with this task (Kraut, Kremen, et al., 2002).

We hypothesize that the contemporaneous surface and deep EEG power changes reflect communication between pre-SMA and the thalamus. The high beta EEG power changes recorded at both the dorsomedial frontal regions and the thalamus appear to reflect closely coordinated communication between these structures, as demonstrated by a functional connectivity analysis using task related fcMRI for the SORT task (Assaf et al., 2009). One caveat regarding this posited corticothalamic interaction is that the intracranially recorded data did not incorporate clear time markers to establish the temporal sequence in which the signals recorded from the two sites arose, so we cannot assert with optimal confidence the direction of signal propagation between these two regions at this point. This fcMRI study of the SORT task provided evidence for a dedicated pre-SMA–thalamus network, which was associated with the so-called “default mode” network (Assaf et al., 2009). This suggests that when shifting into task mode of retrieving an object from features, close intercommunication between the pre-SMA and thalamus is essential. The remaining networks detected in the analyses correspond to semantic memory subsystems that have been proposed to encode representations of object components or properties.

In the previously discussed patient with intracranial and scalp EEG recordings, there was also strong phase correlation between

the high beta power changes detected at the thalamus and the power changes at roughly the same frequency detected at occipital scalp electrodes, corresponding to the visual “what system” in the occipital regions. The 25 Hz interactions between pre-SMA and other brain regions that we have recorded may reflect a thalamically propagated signal to cortical structures indicating a successful termination of the search and retrieval of the integrated object memory.

In summary from the SORT task findings we posit: (1) there is a theta increase in pre-SMA and posterior cortices, starting at approximately between 100–150 ms and continuing throughout the task completion regardless of whether or not the stimuli are both features of a common object, that initiates and longitudinally supports aspects of the semantic object search from the initial feature stimuli presentation, (2) an ERP difference between retrievals and nonretrievals best recorded at the left frontotemporal regions at 750 ms, that reflects semantic relatedness of the feature stimuli in retrievals and unrelatedness of the features in nonretrievals, and (3) later in the course of the task at 1100 ms, there are contemporaneous high beta EEG power increases at pre-SMA, the pulvinar and the occipito-temporal cortices that indexes termination of the search by the successful retrieval of a unique object relating the two input stimuli features. This retrieval process to an integrated memory is aided by caudate-mediated reinforcement of thalamo-cortical transmissions maintaining the correct object’s associated representations and suppressing incorrect competing object component memories.

3. Semantic inhibition tasks (ERPs, time-dependent theta-band EEG power changes, and EEG coherence)

The above studies have focused on the process of retrieving a stored, integrated semantic object memory. An important part of the retrieval process subsumes identification and selection of the correct object to retrieve. Specifically, it is important to be able to identify objects at a basic level (dog), supraordinate category level (animal) and subordinate category level (beagle). These different levels of object identification and/or categorization rely differentially on semantic and perceptual processing. Specifically, categories at the supraordinate level are more abstract and less perceptually based than categories at the basic or subordinate levels, and to quickly identify an object as a “dog” might engage semantic memory differently than when identifying the same object as an “animal”. The processing engaged by object selection and identification informs the object retrieval circuit and allows for manipulation of the semantic (object identification, categorization) and perceptual processing in order to define further the retrieval network. Inhibition of incorrect responses during the NoGo trials also helps to refine the retrieval model in terms of identifying factors associated with suppressing incorrect responses. To study this, we recorded EEG and Event Related Potentials (ERPs) as subjects performed a series of three Go/NoGo motor response tasks that vary in their degree of semantic complexity (Maguire et al., 2009). The first task required the subject to make a Go/NoGo decision based on pictures of one particular car or one particular dog. The second used pictures of different types of cars and of dogs were used. In the final task, subjects made a Go/NoGo decision based on pictures of multiple types of objects (Go condition) and animals (No-Go condition) (Fig. 3).

We found that the N2 response (a scalp surface-negative polarity ERP component with a peak at close to 200 ms after stimulus onset), often associated with inhibition of the motor response, did not change significantly with semantic complexity of the task (Fig. 4). In contrast, the P3 (a positive polarity ERP component with a peak at close to 300 ms after stimulus onset) NoGo amplitude was attenuated by semantic level of the stimuli in all three tasks.

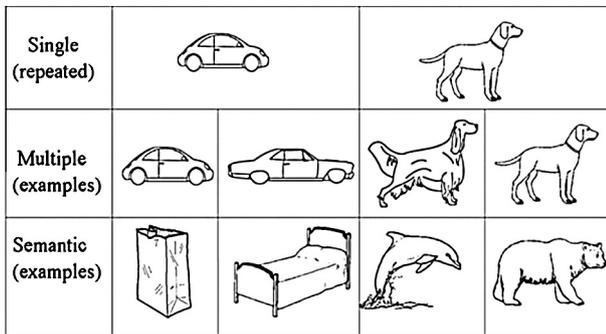


Fig. 3. Examples of the stimuli for the three different Go/NoGo tasks. In the single car–dog condition, 80% of the stimuli are the one car shown and 20% the one dog shown in the figure. For the multiple car–dog task, there are 80% cars, with multiple exemplars of different styles of cars all with the same visual complexity. There are 20% dogs, with multiple dog exemplars drawn of comparable visual complexity. For the semantic task, the 80% of stimuli are objects from multiple categories with varying degrees of semantic relatedness to animals (e.g., food, body parts vs. kitchen items, tools). The 20% of stimuli are animals with a variety of visual typicality (e.g., snake, dolphin, bear) to a four-legged animal so that categorization as animals could not be performed on a simple perceptual characteristic. The familiarity and typicality of items in the animal stimuli were matched to items from each of the distractor categories.

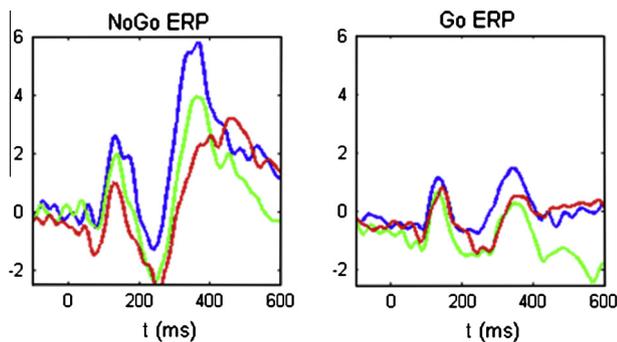


Fig. 4. ERP grand average at Fz across the three inhibition tasks: single (blue), multiple (green), and semantic (red). As can be seen in this depiction there is a decrease in the amplitude of the P3 with task difficulty.

Furthermore, the P3 NoGo peak latency occurred significantly later for the task that required object categorizations (task consisting of, ‘Don’t push for animals,’ where the stimuli consisted of objects and animals) compared to the other two object level identification tasks (Fig. 4). Thus, the semantic complexity/representation level of the stimuli, and the processes that are contingent upon the semantic retrieval, provide useful markers of object retrieval and of contingent motor response inhibition (Maguire et al., 2009). The N2 and P3 ERP components were largest over the midline frontal region that approximates anatomically the location of pre-SMA. Importantly, as per our discussion of the 750 ms left fronto-temporal potential, we cannot assert with complete confidence that the generators of these waveforms lie exclusively subjacent to these scalp locations. It is clearly possible that activity in other nearby cortical regions or less likely subcortical regions that contain cellular generators of appropriate geometry could be contributing to these ERP features.

The temporal patterns and inter-regional coherence of EEG power changes of these three semantic inhibition tasks provide measures of selection and inhibition processes in addition to those that can be derived from ERP (Brier et al., 2010). Analysis of the time-dependent spectral properties of the EEG data demonstrated two brain regions engaged by the inhibitory (NoGo) trials – the frontal pole and pre-SMA regions. These two regions exhibited

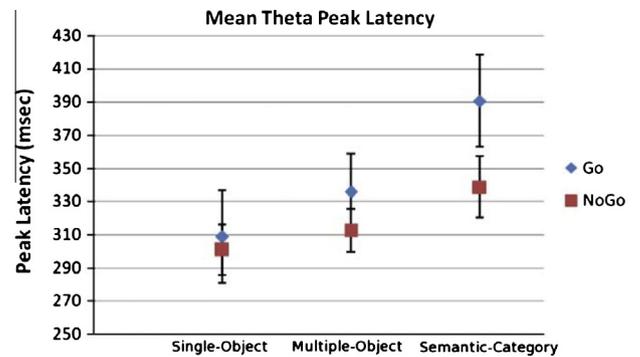


Fig. 5. The peak theta latency depicted for the Gos and NoGos for all three inhibition tasks. The latencies are similar for the single-object and multiple-object tasks and a significant increase in latency for the semantic-category task.

theta band EEG power increases over baseline for NoGo responses that diminished in amplitude with increasing semantic complexity (Fig. 5). The ‘Go’ trials for these three tasks resulted in no significant differences in theta amplitude across tasks of varying semantic complexity. There was a theta peak latency delay only in the task that required processing at the level of semantic supraordinate category representation (categories of *objects* and *animals*) compared to the other two object level tasks for Go responses (Fig. 5). This finding is concordant with the P3 latency effects noted in the ERP analyses of these same tasks.

We further explored the linkages between the pre-SMA and the frontal pole regions using measures of inter-regional coherence (Brier et al., 2010). There was significant theta-band coherence between the frontal pole and pre-SMA for the NoGo conditions across tasks. In addition, this coherence of the theta-band electrical activity between the frontal pole and pre-SMA did not change with semantic level of difficulty, even though amplitudes and latencies varied.

These data indicate that correctly identifying and selecting an object or inhibiting selection of a non-target is reflected in theta frequency band electrical interactions between the frontal pole and pre-SMA in these types of tasks. The amplitudes of both the P3 and theta power changes at pre-SMA are greater with the semantically shallow (single dog, single car) processing condition. We hypothesize that when the prepotent response is strong (semantically simpler stimuli that rely on perceptual features), a stronger inhibitory signal is required to actually stop the response, i.e., higher P3 and theta amplitudes with shallower semantic processing requirements. In addition, the latency of the theta power change is significantly prolonged when more complex, abstract semantic level processing is engaged for the ‘Gos’, implying that the signal from pre-SMA is delayed by category level processing. As the functions may differ between these Go/No tasks and the feature to object retrieval task and theta power changes can subsume a variety of roles even while emanating from the same source region, these Go/NoGo theta changes can inform the role that theta power can subsume in object memory retrieval.

In principle, all of these measures afford further insight into the role or roles played by pre-SMA in object memory retrieval. Depending upon the functional context, pre-SMA has been hypothesized to elaborate ‘stop’ signals (Aron, 2011; Floden & Stuss, 2006; Picton et al., 2006), to mediate conflict resolution (Aron, Behrens, Smith, Frank, & Poldrack, 2007) or a combination that incorporates aspects of both, i.e., a dual role of response inhibition and response selection (Mostofsky & Simmonds, 2008; Simmonds, Pekar, & Mostofsky, 2007). Again depending upon the context, caudate modulation of interactions between pre-SMA and the thalamus or pre-SMA and more posterior cortical regions could

suppress incorrect objects and enhance representations of the correct object, followed by termination of the retrieval process (Crosson et al., 2007), similar to the dual role proposed by Mostofsky and Simmonds (2008). In addition, the P3 amplitude and latency and theta latency for the Go trials of the most semantically difficult task suggests that pre-SMA functions may be modified by semantic level of processing. These findings of variable semantic influences on the pre-SMA provide insights into what tasks engage the retrieval circuit (see below). Manifestations of the response selection and inhibition aspects of these operations inform what may be reflected in the 25 Hz and the 4 Hz EEG power changes that are apparent in our data from both the SORT and semantic inhibition tasks.

4. Studies of patients with semantic retrieval deficits

Further insights into this circuit come from the study of patients with brain injury and disease. These studies suggest a possible modulating role of the thalamus and how dysfunction in the thalamus affects object retrieval. We used the SORT task and fMRI to evaluate veterans of the 1991 Gulf War who reported word-finding deficits (Calley et al., 2010). In 38 Gulf War veterans in three affected groups (Gulf War Syndromes 1, 2, and 3) and in normal deployed controls, we found between-group differences in thalamic activity. Patients with Syndromes 1 and 2 complained of word finding impairments, and showed significant thalamic fMRI signal differences from each other and from controls. We found that fMRI signal changes in the thalamus correlated with accuracy and reaction time during task performance across all groups, providing further evidence that thalamic function is essential to effective semantic memory retrieval and is disrupted to varying degrees in these patients. However, in the most impaired patients, who made more errors and had longer reaction times, we showed that as reaction times increased, there was an increase in thalamic BOLD signal, whereas the typical response was a decrease in BOLD signal change as reaction times increased (Fig. 6). These findings demonstrate that thalamic dysfunction correlates with object memory retrieval errors and suggest that such dysfunction can also lead to delayed responses even if those responses are correct. Thalamic pathology has been reported in Gulf War Illness (Abou-Donia

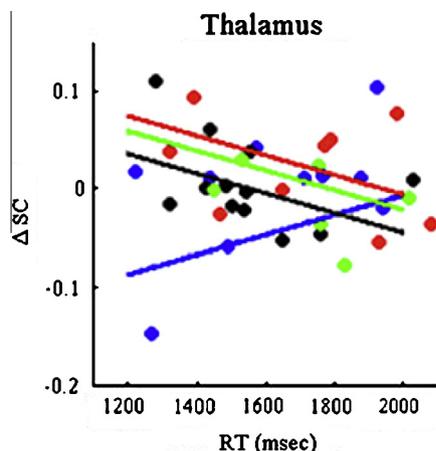


Fig. 6. Analysis of covariance (ANCOVA) for fMRI performance of the SORT task in patients with Gulf War Illness (GWI). The graph shows the effect of Gulf War Illness group membership on the correlation between % signal change (SC) and reaction time (RT) within the thalamus. The blue line represents GWI Haley syndrome 2 patients who complain of and have deficits in word finding and the black line designates controls, red for syndrome 1, and green for syndrome 3. The GWI syndrome 2 patients have a dysfunctional correlation of increasing percent signal change with increasing reaction time, compared to the normal controls and other syndromes with less prominent word finding complaints.

et al., 2004), but dysfunction was not correlated with performance as in Calley et al. (2010). Previous studies of rats exposed to stress, pyridostigmine bromide, DEET, and permethrin, similar to the pattern of exposures that led to Gulf War Syndrome, resulted in thalamic cell loss and selective disruption of the blood–brain–barrier (Abdel-Rahman, Shetty, & Abou-Donia, 2002). Thalamic cell loss and/or reduced cellular activity in the Gulf War Illness patients could result in the altered BOLD patterns and impaired performance seen in these patients. We also have reported on a patient with a thalamic CVA (an extreme level of neuronal damage) who could not perform the SORT task at all and whose speech was characterized by pronounced word finding difficulties and ‘empty speech’ in terms of nouns (Segal, Williams, Kraut, & Hart, 2003).

Studies have demonstrated lexical–semantic deficits in general with posterior thalamic lesions (Metter et al., 1988; Johnson & Ojemann, 2001). Further studies of vascular lesions in the thalamus suggest that anomia is the most prevalent language deficit, which is thought to reflect damage to networks subserving functions ranging from attentional gating to working memory (Nadeau & Crosson, 1997; Schmahmann, 2003). A case of a category specific perceptual/sensory deficit from a thalamic lesion led to the suggestion that the thalamus functions as an integrator of perceptual and semantic processing (Levin, Ben-Hur, Biran, & Wertman, 2005). The pre-SMA is connected to the caudate via the medial subcallosal white matter fasciculus. Lesions affecting this white matter tract in stroke patients have resulted in a nonfluent aphasia with poor recovery of spontaneous speech (Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, & Albert, 1989; Naeser et al., 1998). Intraoperative electrical stimulation of this tract consistently produces an anomia and reduced spontaneous speech (Duffau et al., 2002).

Further insights into the retrieval circuit have been provided through study of basal ganglia pathology. Controls and patients with cortical lesions still maintain the facilitation effect in retrieving and selecting the correct meanings of items, while patients with vascular lesions in the basal ganglia and those with Parkinson’s disease lose the facilitation effect (Copland, 2003). This finding may reflect failure of attention or inhibitory mechanisms, or suboptimal inhibition/suppression that the caudate typically provides. This latter account is most consistent with our model.

5. Summary of pre-SMA–caudate–thalamic circuit

While we propose that the pre-SMA–thalamic circuit plays a role in the retrieval of an integrated object concept in semantic memory, we acknowledge that this is not the only neural circuit for semantic retrieval (Crosson et al., 1999, 2003) and that this circuit may not be specific to semantic memory alone. A circuit that includes pre-SMA, thalamus, and caudate has also been shown to be active in tasks of episodic memory retrieval (Bastin et al., 2012; Wiggs, Weisberg, & Martin, 1999), and a circuit that includes the thalamus and the caudate appears to play a role in the retrieval of autobiographical memory (Burianova & Grady, 2007).

In our feature to object retrieval task (SORT), pre-SMA elicits a theta-band EEG power increase that extends to the parieto-occipital cortices starting at approximately between 100–150 ms and that is sustained throughout the task. We posit that this activity indexes initiation of the controlled object search and selectively engages the mechanism through which inter-regional communication is mediated or at least facilitated (Ketteler, Kastrau, Vohn, & Huber, 2008; Picard & Strick, 1996). There is a 750 ms ERP divergence detected at the left fronto-temporal region that reflects the difference between features that are semantically related as opposed to feature pairs that are unrelated. Activation of the cortical representations of the correct semantic target object and its components (e.g., features, category membership, etc.) is accentuated and prolonged via the direct loop of the basal ganglia extending from

the caudate to thalamus, resulting in enhancing thalamo-cortical activity. The indirect caudate loop suppresses the activity in cortical representations of incorrect objects, leading to their nonretrieval. As the cortical representations of multiple components of the correct object emerge, there is interaction between pre-SMA, thalamus, and parieto-occipital cortical regions at around 1100 ms that is represented by changes in high beta band EEG power increase and that designates the end of the object search process and resultant object memory retrieval with coactivation of the object related representations (Fig. 7). We believe that at least in a cued task, pre-SMA initiates operation of this retrieval mechanism (Crosson et al., 2003; Hoshi & Tanji, 2004; Isoda & Hikosaka, 2007). We further propose that during the search process, pre-SMA–thalamo-cortical oscillations, including facilitation of activity in circuits that mediate access to correct representations and suppression activity in circuits that mediate access to incorrect ones, persist until activation of a correlated set of components emerges as the correct target. Upon coordinated activation of features that comprise the correct object, we posit that pre-SMA governs termination of the search, with the resultant coactivation of the object component representations signifying the integrated object memory. We acknowledge that this circuit may be engaged in other tasks requiring semantic retrieval, with the time course of the above proposed semantic retrieval components may differ in other tasks from the SORT that was used here to delineate this circuit.

Our EEG and ERP recordings from the semantic inhibition experiments provide further insight into the multiple signals originating from pre-SMA as related to semantic processing and semantic factors that influence these signals. The 'Go' trials in our Go/NoGo studies show no significant change in theta power amplitude across the range of semantically-contingent tasks, indicating that the neural signal from pre-SMA in identifying/selecting an object is the same across conditions. However, the latency of the selecting theta signal is significantly longer with the object-animal (category-level) task, compatible with the notion that the temporal activation of pre-SMA is influenced by the level of semantic processing (only the object animal task requires supraordinate categorization to perform the task).

The P3, theta and coherence measures recorded during the NoGo trials provide evidence for how frontal polar cortical regions interact with pre-SMA when identifying and selecting target objects in the context of distractors. There appears to be significant

frontal pole influence on pre-SMA across all three tasks as indexed by similar coherence of the theta signal. However, pre-SMA's role in identifying/selecting an object is influenced by the types of distractors and by whether the object identification/selection task involves supraordinate category level engagement. Thus, greater semantic complexity and level of processing (e.g., category) can delay the activation of pre-SMA's neural signal (Fig. 7).

The role imputed to the thalamus in this circuit is supported by studies in cats showing that the pulvinar sends signals in the high beta/gamma frequency range to visual cortices for either visual object attention or binding for object recognition (Sherman & Guillery, 2002). Multiple studies have suggested a cortico-thalamic–cortical circuit in visual attention. An important component of the circuit is the pulvinar synchronization of primary and non-primary visual cortices via high beta/gamma EEG rhythms propagated through two distinct corticothalamic pathways (Bekisz & Wrobel, 1999; Sherman & Guillery, 2002; Shipp, 2003; Wrobel, Ghazaryan, Bekisz, Bogdan, & Kaminski, 2007). The pulvinar complex has also been shown in cats to signal the visual primary and association cortices for visual attention and for binding features together for object recognition via two distinct gamma signals (Shumikhina & Molotchnikoff, 1999). In humans, it has been beta (as opposed to gamma) synchronization that has been noted in attention tasks across multiple cortical regions (Gross et al., 2004; Kopell, Ermentrout, Whittington, & Traub, 2000), and it has been proposed that synchronization (or desynchronization) of these beta rhythms spatially linking distant cortical regions accounts for other aspects of cognition (Jones, 2001). In cats, these frequency synchronizations circuits have been proposed to proceed temporally as cortico-thalamic–cortical circuits, with the first cortical region typically being primary sensory (e.g., visual) cortices. However, in semantic memory in humans, the first cortical region we propose is the pre-SMA. Jones (2001) has suggested that in humans, the first cortical 'drivers' of beta synchronization cortico-thalamic–cortical circuits are prefrontal regions. This signal would then project to the matrix cells of a thalamic relay nucleus (pulvinar), which would in turn project to other populations of cortical cells and thus coordinate or bind together the activities of multiple cortical regions (Usrey & Reid, 1999; Llinás & et al., 1998; Jones, 2001). Wahl et al. (Wahl et al., 2008) recorded from thalamic, basal ganglia and cortical electrodes during sentence presentation for semantic or syntactic decisions and determined that

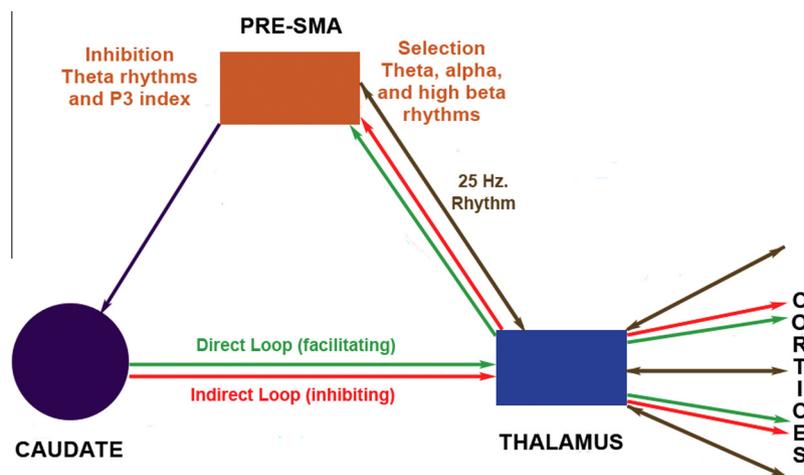


Fig. 7. Schematic of pre-SMA–caudate–thalamus circuit for semantic memory retrieval. The high beta rhythms (~25 Hz rhythms) communicate between pre-SMA, thalamus, and cortices as noted (brown arrows). The 'selection' and 'inhibition' notations designate factors that modulate pre-SMA function that were derived from the semantic inhibition tasks (orange text). The caudate functions to facilitate correct target cortical activations through the thalamus via the direct loop (green color arrows) and to inhibit incorrect targets cortical activations via the indirect loop (red color arrows).

pre-SMA and thalamus were engaged in semantic processing, while basal ganglia were not. The ERP time courses overlapped between the thalamus and cortices during a semantic sentence incongruities task, precluding determination of the direction of information flow between these regions. This was interpreted to suggest that the thalamus functions to organize intercortical communication between distributed semantic networks. Again, this circuit may not be exclusive to semantic processing given that pre-SMA and thalamus were also involved when there were syntactic violations (Wahl et al., 2008).

An important question is what semantic operations engage this mechanism or specific aspects of it. We propose that the pre-SMA–thalamus–caudate circuit is engaged for complex, controlled semantic search and retrieval. This notion extends from the proposition that the thalamus and basal ganglia (caudate) are engaged by higher-order language processing that cannot rely on automatic processing, but which recruits controlled processes and might reflect a strategic semantic search mechanism (Ketteler et al., 2008). When switching between languages in bilinguals, there is selective engagement of the caudate, thought to be necessitated by controlled, compared to automatic, processing (Abutalebi et al., 2008; Crinion et al., 2006; Friederici, 2006; Gil Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005; Grogan, Green, Nilufa, Crinion, & Price, 2009). Other semantic operations that engage the circuit include rule-based but not similarity based categorization (Grossman et al., 2003); complex categorization tasks (Gotts, Milleville, Bellgowan, & Martin, 2010); sentence comprehension with metaphor abstraction (Stringaris, Medford, Giampietro, Brammer, & David, 2007); and category driven word generation (Basho, Palmera, Rubion, Wulfecke, & Muller, 2007; Crosson et al., 2003). While each of these processes engages a frontal–subcortical circuit, it is notable that retrieval processes are present both for searches for comprehension of input and production of output. Other higher-order linguistic tasks such as phonological learning (Tricoli, Delgado, McCandliss, McClelland, & Fiez, 2006), second language phonemic search (Grogan et al., 2009) also engage aspects of this circuit, each of which may be considered controlled, not automatic, processing. Semantic tasks that engage only simple, automatic retrieval processing such as simple categorization tasks (Kraut, Kremen, et al., 2002; Kraut, Moo, et al., 2002) and simple word generation tasks (Tremblay & Gracco, 2006; Grogan et al., 2009) have not elicited detectable activity in this circuit.

Additional predictions that are generated from this model are that damage to the pre-SMA, or white matter connections to pre-SMA (especially if this damage is bilateral) would result in object memory retrieval proceeding more slowly and, especially in a timed task or one in which stimuli are presented rapidly, less accurately. Damage to caudate, or white matter pathways leading either into or out of it we would predict would increase the likelihood of false positive results on tasks such as in the SORT test we have employed to probe object memory. While predictions based on thalamic damage are difficult given the rich intrathalamic as well as thalamocortical connections, damage to thalamic areas engaged in synchronizing multiple, modality-specific, cortical regions encoding object subcomponents will yield errors in tasks like the SORT yet may not disrupt task performance that do not require this multiple modality integration.

There are alternative explanations and specific questions of timing and signal direction that we acknowledge are open to interpretation with this model. First, the directionality of the high beta pre-SMA–thalamus and thalamus–occipital electrode signals cannot be determined with certainty. Nor can the timing of the thalamic high beta signal. Those data were obtained from the single subject with thalamic depth electrodes and the assertions made in our model were made by correlating with the findings from

scalp EEG recordings of normal controls. Other studies investigating the multiple functions and electrophysiological correlates of pre-SMA have suggested sequences of electrophysiological activity similar to what we have proposed. In an electrocorticographic study of a patient performing a simple visual ‘Stop/Go’ task, preparing to stop was correlated with increased high gamma amplitude in pre SMA, which preceded by ~750 ms similar frequency activity in the right inferior frontal gyrus. Upon actually stopping, there was an increase in beta band activity (~16 Hz) in both regions, with significantly stronger inter-regional coherence (Swann et al., 2012).

Also yet to be clarified are the specific cognitive operations associated with the high beta activity for retrievals at 1100 ms. Retrieval of an integrated semantic object memory in our model starts with initiation of the search process, termination of that search process, and retrieval of the integrated memory via coactivation of feature and category representational components. Characterizing the details of these operations and better specifying the cortical and subcortical structures that perform them requires further investigation.

Overall, the proposed model is in keeping with Crosson’s model of selective engagement (Crosson et al., 2003; Nadeau & Crosson, 1997) which proposes that pre-SMA–thalamic networks are engaged in semantic processing, and that the basal ganglia perform a nonlinguistic role of facilitation and suppression of correct and incorrect choices, respectively. The present model is also consistent with the selective engagement model’s proposal that the thalamus can function to gate informational flow (Nadeau & Crosson, 1997). The selective engagement aspect of the model is also consistent with the thalamus’ role in the gating and coordination of semantic activations distributed across widespread cortical connections (Kraut, Kremen, et al., 2002; Kraut, Moo, et al., 2002; Kraut et al., 2003). The present model is also consistent with Wahl et al.’s (2008) assertions that thalamic structures can assume the role of monitoring intercortical communication, and that at least certain semantic functions studied here are engaged in cortico-thalamic processing.

Although there are still many unanswered questions about the nature of the cortico-subcortical and corticocortical interactions we have proposed, we believe the model we have begun to construct provides a framework that will guide refinements, extensions and corrections of understanding how semantic memory is organized and processed in the brain.

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References

- Abdel-Rahman, A., Shetty, A. K., & Abou-Donia, M. B. (2002). Disruption of the blood–brain barrier and neuronal cell death in cingulate cortex, dentate gyrus, thalamus, and hypothalamus in a rat model of Gulf War syndrome. *Neurobiology of Diseases*, 10(3), 306–326.

- Abou-Donia, M. B., Dechkovskaia, A. M., Goldstein, L. B., Abdel-Rahman, A., Bullman, S. L., & Khan, W. A. (2004). Co-exposure to pyridostigmine bromide, DEET, and/or promethrin causes sensorimotor deficit and alterations in acetylcholinesterase activity. *Pharmacology, Biochemistry and Behavior*, 77(2), 253–262.
- Abutalebi, J., Annoni, J. M., Zimine, I., Pegna, A., Seghier, M., Lee-Jahnke, H., et al. (2008). Language control and lexical competition in bilinguals: An event-related fMRI study. *Cerebral Cortex*, 18, 1496–1505.
- Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience*, 27, 3743–3752.
- Aron, A. R. (2011). From reactive to proactive and selective control: Describing a richer model for stopping inappropriate responses. *Biological Psychiatry*, 69(12), 55–68.
- Assaf, M., Calhoun, V. D., Kuzu, C. H., Kraut, M. A., Rivkin, P. R., Hart, J., et al. (2006). Neural correlates of the object-recall process in semantic memory. *Psychiatry Research: Neuroimaging Section*, 147(2), 115–126.
- Assaf, M., Jagannathan, K., Calhoun, V., Kraut, M., Hart, J., Jr., & Pearlson, G. (2009). Temporal sequence of hemispheric network activation during semantic processing: A functional network connectivity analysis. *Brain and Cognition*, 70(2), 238–246.
- Basho, S., Palmera, E., Rubion, M., Wulfecke, B., & Muller, R. (2007). Effects of generation mode in fMRI adaptations of semantic fluency: Paced production and overt speech. *Neuropsychologia*, 45(8), 1697–1706.
- Bastin, C., Feyers, D., Majerus, S., Baletau, E., Degueldre, C., Luxen, A., et al. (2012). The neural substrates of memory suppression: A fMRI exploration of directed forgetting. *PLoS One*, 7(1), Epub.
- Bekisz, M., & Wrobel, A. (1999). Coupling of beta and gamma activity in corticothalamic system of cats attending to visual stimuli. *NeuroReport*, 10, 3589–3594.
- Beauchamp, M. S., Lee, K. E., Argall, B. D., & Martin, A. (2004). Integration of auditory and visual information about objects in superior temporal sulcus. *Neuron*, 41(5), 809–823.
- Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, 12, 2767–2796.
- Brier, M. R., Maguire, M. J., Tillman, G. D., Hart, J., Jr., & Kraut, M. A. (2008). Event-related potentials in semantic memory retrieval. *Journal of the International Neuropsychological Society*, 14(5), 815–822.
- Brier, M. R., Ferree, T. C., Maguire, M. J., Moore, P., Spence, J., Tillman, G. D., et al. (2010). Frontal theta and alpha power and coherence changes are modulated by semantic complexity in Go/NoGo tasks. *International Journal of Psychophysiology*, 78(3), 215–224.
- Burianova, H., & Grady, C. (2007). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *Journal of Cognitive Neuroscience*, 19(9), 1520–1534.
- Calley, C. S., Motes, M., Chiang, H. -S., Buhl, V., Spence, J., Abdi, H., et al. (in press). Threat as a feature in visual semantic object memory. *Human Brain Mapping*.
- Calley, C. S., Kraut, M. A., Spence, J. S., Briggs, R. W., Haley, R. W., & Hart, J., Jr. (2010). The neuroanatomic correlates of semantic memory deficits in patients with Gulf War illnesses: A pilot study. *Brain Imaging and Behavior*, 4(3–4), 248–255.
- Caramazza, A., Hillis, A., & Rapp, B. (1990). The multiple semantics hypothesis: Multiple confusions? *Cognitive Neuropsychology*, 7, 161–189.
- Caramazza, A., & Shelton, J. R. (1998). Domain-specific knowledge systems in the brain the animate–inanimate distinction. *Journal of Cognitive Neuroscience*, 10, 1–34.
- Copland, D. A. (2003). Basal ganglia and semantic engagement. *Journal of the International Neuropsychological Society*, 9, 1041–1052.
- Copland, D. A., Chenery, H. J., & Murdoch, B. E. (2000). Processing lexical ambiguities in word triplets: Evidence of lexical–semantic deficits following dominant nonthalamic subcortical lesions. *Neuropsychology*, 14, 379–390.
- Copland, D. A., Chenery, H. J., & Murdoch, B. E. (2001). Discourse priming of homophones in individuals with dominant subcortical lesions, cortical lesions, and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, 23, 338–356.
- Crinion, J., Turner, R., Grogan, A., Hanakawa, T., Noppeney, U., Devlin, J., et al. (2006). Language control in the bilingual brain. *Science*, 312, 1537–1540.
- Crosson, B. (1999). Subcortical mechanisms in language: Lexical–semantic mechanisms and the thalamus. *Brain and Cognition*, 40(2), 414–438.
- Crosson, B., Sadek, J., Bobholz, J., Gökçay, D., Mohr, C., Leonard, C., et al. (1999). Activity in the paracingulate and cingulate sulci during word generation: An fMRI study of functional anatomy. *Cerebral Cortex*, 9(4), 307–316.
- Crosson, B., Sadek, J. R., Maron, L., Gökçay, D., Mohr, C. M., Auerbach, E. J., et al. (2001). Relative shift in activity from medial to lateral frontal cortex during internally versus externally guided word generation. *Journal of Cognitive Neuroscience*, 13, 272–283.
- Crosson, B., Benefield, H., Cato, M. A., Sadek, J. R., Moore, A. B., Wierenga, C. E., et al. (2003). Left and right basal ganglia and frontal activity during language generation: Contributions to lexical, semantic and phonological processes. *Journal of the International Neuropsychological Society*, 9(7), 1061–1077.
- Crosson, B., Benjamin, M., & Levy, I. (2007). Role of the basal ganglia in language and semantics: Supporting cast. In J. Hart & M. Kraut (Eds.), *Neural substrates of semantic memory*. Cambridge, UK: Cambridge University Press.
- Damasio, A. R. (1990). Category-related recognition deficits as a clue to the neural substrates of knowledge. *Trends in Neuroscience*, 13, 95–98.
- Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience*, 15, 5870–5878.
- Duffau, H., Capelle, L., Sichez, N., Denvil, D., Lopes, M., Sichez, J.-P., et al. (2002). Intraoperative mapping of the subcortical language pathways using direct stimulations: An anatomo-functional study. *Brain*, 125(Pt. 1), 199–214.
- Ferree, T. C., Brier, M. R., Hart, J., Jr., & Kraut, M. A. (2009). Space–time–frequency analysis of EEG data using within-subject statistical tests followed by sequential PCA. *NeuroImage*, 45(1), 109–121.
- Fiez, J. A. (1997). Phonology, semantics, and the role of the left inferior prefrontal cortex. *Human Brain Mapping*, 5, 79–83.
- Floden, D., & Stuss, D. T. (2006). Inhibitory control is slowed in patients with right superior medial frontal damage. *Journal of Cognitive Neuroscience*, 18, 1843–1849.
- Friederici, A. (2006). What's in control of language. *Nature Neuroscience*, 9(8), 991–992.
- Gainotti, G. (2000). What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: A review. *Cortex*, 36, 539–559.
- Gil Robles, G., Gatignol, P., Capelle, L., Mitchell, M. C., & Duffau, H. (2005). The role of dominant striatum in language: A study using intraoperative electrical stimulation. *Journal of Neurology, Neurosurgery and Psychiatry*, 76(7), 940–946.
- Gollo, L., Mirasso, C., & Villa, A. (2010). Dynamic control for synchronization of separated cortical areas through thalamic relay. *NeuroImage*, 52, 47–955.
- Gotts, S., Millerville, S., Bellgowan, P., & Martin, A. (2010). Broad and narrow conceptual tuning in the human frontal lobes. *Cerebral Cortex*, 21, 477–491.
- Grogan, A., Green, D., Nilufa, A., Crinion, J., & Price, C. (2009). Structural correlates of semantic and phonemic fluency ability in first and second languages. *Cerebral Cortex*, 19, 2690–2698.
- Gross, J., Schmitz, F., Schnitzler, I., Kessler, K., Shapiro, K., Hommel, B., et al. (2004). Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *PNAS*, 101(35), 13050–13055.
- Grossman, M., Smith, E., Koenig, P., Glosser, G., DeVita, C., Moore, P., et al. (2003). The neural basis for categorization in semantic memory. *NeuroImage*, 17, 1549–1561.
- Gutierrez, C., Cola, M. G., Seltzer, B., & Cusick, C. (2000). Neurochemical and connective organization of the dorsal pulvinar complex in monkeys. *The Journal of Comparative Neurology*, 419(1), 61–86.
- Hart, J., Jr., Berndt, R. S., & Caramazza, A. (1985). Category-specific naming deficits following cerebral infarction. *Nature*, 316, 439–440.
- Hart, J., Jr., & Gordon, B. (1990). Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. *Annals of Neurology*, 27(3), 226–231.
- Hart, J., Jr., & Gordon, B. (1992). Neural subsystems for object knowledge. *Nature*, 359(6390), 60–64.
- Hart, J., Crone, N., Lesser, R., Sieracki, J., Miglioretti, D., Hall, C., et al. (1998). Temporal dynamics of verbal object comprehension. *Proceedings of the National Academy of Sciences of the United States of America*, 95, 6498–6503.
- Hart, J., Jr., Anand, R., Zoccoli, S., Maguire, M., Gamino, J., Tillman, G., et al. (2007). Neural substrates of semantic memory. *Journal of the International Neuropsychological Society*, 13(5), 865–880.
- Hart, J., & Kraut, M. (2007). Neural hybrid model of semantic object memory. In J. Hart & M. Kraut (Eds.), *Neural substrates of semantic memory*. Cambridge, UK: Cambridge University Press.
- Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, 293(5539), 2425–2430.
- Hillis, A. E., Rapp, B., Romani, C., & Caramazza, A. (1990). Selective impairment of semantics in lexical processing. *Cognitive Neuropsychology*, 7, 191–243.
- Hillis, A. E., Wityk, R. J., Tuffiash, E., Beauchamp, N. J., Jacobs, M. A., Barker, P. B., et al. (2001). Hypoperfusion of Wernicke's area predicts severity of semantic deficit in acute stroke. *Annals of Neurology*, 50, 561–566.
- Hoshi, E., & Tanji, J. (2004). Differential roles of neuronal activity in the supplementary and presupplementary motor areas: From information retrieval to motor planning and execution. *Journal of Neurophysiology*, 92(6), 3482–3499.
- Humphreys, G. W., & Forde, E. M. E. (2001). Hierarchies, similarity, and interactivity in object recognition: “Category-specific” neuropsychological deficits. *Behavioral and Brain Sciences*, 24, 453–509.
- Isoda, M., & Hikosaka, O. (2007). Switching from automatic to controlled action by monkey medial frontal cortex. *Nature Neuroscience*, 10(2), 240–248.
- Johnson, M. D., & Ojemann, G. A. (2001). The role of the human thalamus in language and memory: Evidence from electrophysiological studies. *Brain and Cognition*, 42, 218–230.
- Jones, E. G. (2001). The thalamic matrix and thalamocortical synchrony. *Trends in Neuroscience*, 24(10), 595–601.
- Ketteler, D., Kastrau, F., Vohn, R., & Huber, W. (2008). The subcortical role of language processing. High level linguistic features such as ambiguity–resolution and the human brain: an fMRI study. *NeuroImage*, 39, 2002–2009.
- Kopell, N., Ermentrout, G. B., Whittington, M. A., & Traub, R. D. (2000). Gamma rhythms and beta rhythms have different synchronization properties. *PNAS*, 97(4), 1867–1872.
- Kraut, M. A., Kremen, S., Segal, J. B., Calhoun, V., Moo, L. R., & Hart, J., Jr. (2002). Object activation from features in the semantic system. *Journal of Cognitive Neuroscience*, 14(1), 24–36.
- Kraut, M. A., Moo, L. R., Segal, J. B., & Hart, J., Jr. (2002). Neural activation during an explicit categorization task: Category- or feature-specific effects? *Cognitive Brain Research*, 13(2), 213–220.

- Kraut, M. A., Calhoun, V., Pitcock, J. A., Cusick, C., & Hart, J. Jr., (2003). Neural hybrid model of semantic object memory: Implications from event-related timing using fMRI. *Journal of the International Neuropsychological Society*, 9(7), 1031–1040.
- Kraut, M. A., Pitcock, J., & Hart, J. Jr., (2004). Neural mechanisms of semantic memory. *Current Neurology and Neuroscience Reports*, 4(6), 461–465.
- Kraut, M. A., Pitcock, J. A., Calhoun, V., Li, J., Freeman, T., & Hart, J. Jr., (2006). Neuroanatomic organization of sound memory in humans. *Journal of Cognitive Neuroscience*, 18(11), 1877–1888.
- Levin, N., Ben-Hur, T., Biran, I., & Wertman, E. (2005). Category specific dysnomia after thalamic infarction: A case-control study. *Neuropsychologia*, 43, 1385–1390.
- Llinás, R. et al. (1998). The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 353, 1841–1849.
- Maguire, M. J., Brier, M. R., Moore, P. S., Ferree, T. C., Ray, D., Mostofsky, S., et al. (2009). The influence of perceptual and semantic categorization on inhibitory processing as measured by the N2–P3 response. *Brain and Cognition*, 71(3), 196–203.
- Mahon, B. Z., & Caramazza, A. (2003). Constraining questions about the organisation and representation of conceptual knowledge. *Cognitive Neuropsychology*, 20, 433–450.
- Marín, G., Duran, E., Morales, C., González-Cabrera, C., Sents, E., Mpodozis, J., et al. (2012). Attentional capture? Synchronized feedback signals from the isthmi boost retinal signals to higher visual areas. *Journal of Neuroscience*, 32(3), 1110–1122.
- Metter, E. J., Riege, W., Hanson, W., Jackson, C., Kempler, D., & van Lanker, D. (1988). Subcortical structures in aphasia. *Archives of Neurology*, 45, 1229–1234.
- Miceli, G., Fouch, E., Capasso, R., Shelton, J. R., Tomaiuolo, F., & Caramazza, A. (2001). The dissociation of color from form and function knowledge. *Nature Neuroscience*, 4(6), 627–662.
- Moss, H. E., Tyler, L. K., & Devlin, J. (2002). The emergence of category specific deficits in a distributed semantic system. In E. Forde & G. W. Humphreys (Eds.), *Category-specificity in brain and mind* (pp. 115–148). Sussex: Psychology Press.
- Mostofsky, S. H., & Simmonds, D. J. (2008). Response inhibition and response selection: Two sides of the same coin. *Journal of Cognitive Neuroscience*, 20(5), 751–761.
- Mummery, C. J., Patterson, K., Hodges, J. R., & Price, C. J. (1998). Functional neuroanatomy of the semantic system: Divisible by what? *Journal of Cognitive Neuroscience*, 10(6), 766–777.
- Nadeau, S. E., & Crosson, B. (1997). Subcortical aphasia. *Brain and Language*, 58, 355–402.
- Naeser, M. A., Palumbo, C. L., Helm-Estabrooks, N., Stiassny-Eder, D., & Albert, M. L. (1989). Severe nonfluency in aphasia: Role of the medial subcallosal fasciculus and other white matter pathways in recovery of spontaneous speech. *Brain*, 112(Pt. 1), 1–38.
- Naeser, M. A., Baker, E. H., Palumbo, C. L., Nicholas, M., Alexander, M. P., Samaraweera, R., et al. (1998). Lesion site patterns in severe, nonverbal aphasia to predict outcome with a computer-assisted treatment program. *Archives of Neurology*, 55(11), 1438–1448.
- Perani, D., Cappa, S., Bettinardi, V., Bressi, S., Gorno-Tempini, M., Matarrese, M., et al. (1995). Different neural systems for the recognition of animals and man-made tools. *NeuroReport*, 6, 1637–1639.
- Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, 6, 342–353.
- Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (2006). Effects of focal frontal lesions on response inhibition. *Cerebral Cortex*, 17, 826–838.
- Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science*, 240, 1627–1631.
- Sartori, G., & Job, R. (1988). The oyster with four legs: A neuropsychological study on the interaction of visual and semantic information. *Cognitive Neuropsychology*, 5(1), 105–132.
- Sartori, G., Job, R., Miozzo, M., Zago, S., & Marchiori, G. (1993). Category-specific form-knowledge deficit in a patient with herpes simplex virus encephalitis. *Journal of Clinical and Experimental Neuropsychology*, 15(2), 280–299.
- Schmahmann, J. D. (2003). Vascular syndromes of the thalamus. *Stroke*, 34(9), 2264–2278.
- Segal, J. B., Williams, R., Kraut, M. A., & Hart, J. Jr., (2003). Semantic memory deficit with a left thalamic infarct. *Neurology*, 61(2), 252–254.
- Sherman, S. M., & Guillery, R. W. (2002). The role of the thalamus in the flow of information to the cortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 357, 1695–1708.
- Shipp, S. (2003). The functional logic of cortico-pulvinar connections. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 358, 1605–1624.
- Shumikhina, S., & Molotchnikoff, S. (1999). Pulvinar participates in synchronizing neural assemblies in the visual cortex, in cats. *Neuroscience Letters*, 272, 135–139.
- Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2007). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, 46, 224–232.
- Slotnick, S. D., Moo, L. R., Kraut, M. A., Lesser, R. P., & Hart, J. Jr., (2002). Interactions between thalamic and cortical rhythms during semantic memory recall in human. *Proceedings of the National Academy of Sciences of the United States of America*, 99(9), 6440–6443.
- Stringaris, A., Medford, N., Giampietro, V., Brammer, M., & David, A. (2007). Deriving meaning: Distinct neural mechanisms for metaphoric, literal, and non-meaningful sentences. *Brain and Language*, 100, 150–162.
- Swann, N. C., Cai, W., Conner, C. R., Pieters, T. A., Claffey, M. P., George, J. S., et al. (2012). Roles for the pre-SMA and the right inferior frontal gyrus in stopping action: Electrophysiological responses and functional and structural connectivity. *NeuroImage*, 59(3), 2860–2870.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences of the United States of America*, 94, 14792–14797.
- Tremblay, P., & Gracco, V. L. (2006). Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence. *NeuroImage*, 33, 947–957.
- Tricomi, E., Delgado, M. R., McCandliss, B. D., McClelland, J. L., & Fiez, J. A. (2006). Performance feedback drives caudate activation in a phonological learning task. *Journal of Cognitive Neuroscience*, 18, 1029–1043.
- Tyler, L. K., & Moss, H. E. (2001). Towards a distributed account of conceptual knowledge. *Trends in Cognitive Sciences*, 5, 244–252.
- Usrey, W. M., & Reid, R. C. (1999). Synchronous activity in the visual system. *Annual Review of Physiology*, 61, 435–456.
- von Zerssen, G. C., Mecklinger, A., Opitz, B., & von Cramon, D. Y. (2001). Conscious recollection and illusory recognition: An event related study. *European Journal of Neuroscience*, 13, 2148–2156.
- Wahl, M., Marzinzik, F., Friederici, A. D., Hahne, A., Kupsch, A., Schneider, G. H., et al. (2008). The human thalamus processes syntactic and semantic language violations. *Neuron*, 59(5), 695–707.
- Warrington, E. K., & McCarthy, R. A. (1987). Categories of knowledge: Further fractionation and an attempted integration. *Brain*, 110, 1273–1296.
- Warrington, E. K., & Shallice, T. (1984). Category specific semantic impairments. *Brain*, 107, 829–854.
- Wiggs, C., Weisberg, J., & Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia*, 37(1), 102–118.
- Wrobel, A., Ghazaryan, A., Bekisz, M., Bogdan, W., & Kaminski, J. (2007). Two streams of attention-dependent beta activity in the striate recipient zone of cat's lateral posterior-pulvinar complex. *Journal of Neuroscience*, 27(9), 2230–2240.
- Wrobel, A. (2000). Beta activity: A carrier for visual attention. *Acta Neurobiologiae Experimentalis*, 60, 247–260.