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Semantic association investigated with fMRI and independent component analysis

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Abstract

Semantic association, an essential element of human language, enables discourse and inference. Neuroimaging studies have revealed localization and lateralization of semantic circuitry making substantial contributions to cognitive neuroscience. However, due to methodological limitations, these investigations have only identified individual functional components rather than capturing the behavior of the entire network. To overcome these limitations, we have implemented group independent component analysis (ICA) to investigate the cognitive modules used by healthy adults performing fMRI semantic decision task. When compared to the results of a standard GLM analysis, ICA detected several additional brain regions subserving semantic decision. Eight task-related group ICA maps were identified including left inferior frontal gyrus (BA44/45), middle posterior temporal gyrus (BA39/22), angular gyrus/inferior parietal lobule (BA39/40), posterior cingulate (BA30), bilateral lingual gyrus (BA18/23), inferior frontal gyrus (L>R, BA47), hippocampus with parahippocampal gyrus (L>R, BA35/36) and anterior cingulate (BA32/24). While most of the components were represented bilaterally, we found a single, highly left-lateralized component that included the inferior frontal gyrus and the medial and superior temporal gyri, the angular and supramarginal gyri and the inferior parietal cortex. The presence of these spatially independent ICA components implies functional connectivity and can be equated with their modularity. These results are analyzed and presented in the framework of a biologically plausible theoretical model in preparation for similar analyses in patients with right- or left-hemispheric epilepsies.

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Keywords

Semantic decision; language; Independent component analysis (ICA); GLM; Functional magnetic resonance imaging; language network

INTRODUCTION

Language is a uniquely human cognitive function hence its decline or loss is usually devastating to the victim. The first description of an aphasic patient dates back to the nineteenth century (Broca, 1861; Wernicke 1874). Various models of language processing have been developed since then (1–5). In the original description by Broca, the non-fluent aphasic patient experienced a lesion in the left inferior frontal lobe (4). In 1874, Wernicke described patients with posterior superior temporal lobe lesions who presented with fluent speech but made frequent paraphasic errors; they also had naming, auditory comprehension, and repetition impairments (5). Lichtheim later hypothesized that there is a brain region “*where concepts are elaborated*”, the conceptual or semantic processing center in the left hemisphere (3). Based on these and other findings, Geschwind added tertiary association areas including left angular and supramarginal gyri to the language processing model developing what is called today a Wernicke-Lichtheim-Geschwind theory; this model is still in use (2). These observations from acquired aphasias laid the foundation for modern studies with recently developed imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

A variety of fMRI language paradigms have been designed to investigate multifaceted aspects of language processing and can be classified in respect to the type of stimuli and targeted cognitive function (6). In right handed subjects, language lateralization to the left hemisphere has been conclusively established in 90–96% of them based on clinical data and the results of the fMRI and other neuroimaging studies (7). A similar incidence of left-hemispheric language lateralization has been observed in subjects performing a semantic association task (8). While language lateralization, whether tested with semantic or other language tasks is not in dispute, the complexity of the processes associated with semantic decision makes them suitable for exploring the entire language circuitry and associated cognitive functions.

The fMRI task used in the present study is a variant of the semantic decision/tone decision task first introduced by Binder et al. (9). Performance of this task requires perceptual analysis of speech sounds (“phonetic processing”) and retrieval of previously stored semantic information. This process activates the syntactic processing network along with verbal working memory. For the active and control conditions to be performed correctly, mental resources required for low-level auditory processing and maintaining attention need to be recruited (9). In one previous study, a contrast between semantic decision and tone decision detected robust activations in the left lateralized language networks including frontal, posterior superior temporal and angular gyri. The observed lateralization was much stronger for this contrast when compared to the semantic decision – rest contrast (10). The semantic decision/tone decision (SDTD) task has been previously used to investigate not only the language trajectories associated with age in healthy left- and right-handed adults (8,11) but also as means of estimating language lateralization in epilepsy patients undergoing presurgical evaluation (12–14) or to evaluate post-stroke aphasia recovery (15). Furthermore, this highly-reliable fMRI task has shown superior correlation values with intracarotid amobarbital test (IAT) when compared to a covert verb generation fMRI task (14). Hence, as shown in previous studies, the SDTD fMRI task appears to be well suited for language network evaluation in health and disease. Prior to applying the proposed data

analysis methods to a cohort of epilepsy patients (16), an investigation of healthy subjects performing SDTD task is needed in order to establish the performance of the healthy network associated with semantic processing and to hypothesize regarding the effects of chronic, medication-resistant epilepsy on such a network.

Therefore, in this study, we used the SDTD fMRI task and an alternative neuroimaging data analysis method – group independent component analysis (ICA) – to investigate the neural substrates of semantic decision. ICA is a data-driven method capable of investigating the spatial and temporal behavior of fMRI data without an *a priori* defined timecourse or hemodynamic response (17,18). In this method, the timecourse for each brain voxel from each subject is first normalized to a percent signal change from the mean. Thereafter, data are subjected to a two stage data reduction step at subject and group level using principal component analysis (PCA). Data reduction steps are followed by the ICA decomposition which is based on a stochastic algorithm. Therefore, depending on the initial conditions (i.e., the starting point), ICA decomposition can result in different solutions (i.e., different independent components). For this reason, the algorithm is run repeatedly with clustering analysis to determine the most reliable IC components (19). The IC timecourses of these reliable components are further analyzed using Fourier transforms to determine the most task-related components subserving the semantic decision task for the entire group. ICA has been successfully used to investigate the effects of alcohol intoxication on simulated driving (20,21), modular musical perception (22), story comprehension and covert verb generation (23), story listening (24) or verb generation (25). ICA is not predicated upon an expected neural response (26–28). In contrast to ICA, general linear model (GLM) is a model based fMRI data analysis method that can also allow correlations between various error terms (e.g., data noise) (26). In particular, GLM assumes that all brief neural events evoke a hemodynamic response function (HRF) of the same shape and that the time series is modeled as an impulse train of neural events convolved with this fixed-shaped HRF (28). However, considering the within and across subject HRF variations, assuming a fixed shape for the entire population may not be ideal (29,30). The assumption of fixed-shaped HRF is even more concerning when atypical language behavior or cerebro-vascular reactivity is investigated in subjects where the response is expected to be different because of the underlying brain pathology. Finally, the number of cognitive components involved in semantic decision may exceed the number of activated regions identified by these model-based analyses resulting in an oversimplified picture of semantic decision.

Therefore, the main goal of the current investigation was to examine the behavior of the network that underlies the semantic decision in healthy subjects. The previous, hypothesis driven GLM analysis of these data focused on the contrast between tone decision and semantic decision (14). The current ICA approach is different in that it provides explicit information about the main effects of the semantic decision component of the task rather than the contrast between the two conditions. Further, this approach also provides information about the specific components that contribute to semantic decision (31). Therefore, the information provided by ICA is complementary to a standard GLM and can be utilized to corroborate or to strengthen the interpretation of fMRI findings.

In general, speech comprehension, classically associated with left temporal lobe (5), depends on common systems for processing speech sounds (phonology) and word meanings (lexical semantics). According to the *simple view of reading*, word recognition and linguistic comprehension are assumed to be the two basic components of reading comprehension. Further, it is also presumed that the comprehension component of this model (or view) is utilized to make sense out of the linguistic information (32,33). Finally, a recent study has also highlighted the importance of semantic processing in word identification and reading disability (34). Thus, investigating the neural basis of semantic processing has far reaching

implications and may provide insight into different mechanisms subserving the human language system.

To place our analysis in a theoretical framework, we will present our findings in relation to an extended version of Wernicke-Lichtheim-Geschwind model for language processing (2). Recent neuroimaging studies also support a functional segregation of Broca's and Wernicke's areas (35). Thus, as an end-effect of this work, we will propose a cognitive model for semantic decision based on a two-route model for language processing implicating a direct as well as an indirect route between Broca's and Wernicke's areas. In developing this model, we take into account the left lateralization of the language functions observed with many semantic processing tasks; the typical left language lateralization can be attributed to the early structural asymmetries found in the prenatal brain (36,37). Thus, these prenatal neuroanatomical asymmetries are hypothesized to be the driving factor subserving functional lateralization and localization over the course of language development (38). Finally, our results also highlight the advantages of combining both modular and connectionist approaches to investigating cognitive functions.

We expected cognitive components such as auditory, attention, phonological processing, semantic association and verbal memory to be identified in order to establish normative baseline for a semantic language task that could be then utilized to evaluate language processing in a disease state, e.g., epilepsy. Here we present an approach with ICA that circumvents some of the methodological and interpretational difficulties inherent to more conventional analyses of fMRI data and propose a hierarchical cognitive model associated with semantic decision tasks that could be further investigated using functional/effective connectivity analysis techniques such as structural equation modeling (SEM) (39,40) or dynamical causal modeling (DCM) (41).

METHODS

Subjects

Forty nine adult healthy subjects (21 males, 28 females) took part in the study after signing an informed consent approved by the University of Cincinnati Institutional Review Board. Exclusion criteria included previous neurological illness, history of learning disability, head trauma with loss of consciousness, current or past use of psychostimulant medications, pregnancy, or birth at 37 weeks gestational age or earlier. The detailed demographic data of subjects is detailed in Table 1. All subjects were native English speakers; 47 were right-handed, 2 were left-handed according to the Edinburgh Handedness Inventory (42). All subjects were prescreened for any conditions (such as the presence of metallic implants) which would prevent an MRI scan from being acquired. The mean age was 39.3 ± 12.4 (range; 23–59 years). Results of the analysis of the fMRI data using GLM on all these subjects were included in our previous publication (14) and are not discussed in depth here (Figure 1).

Functional MRI task

The SDTD task consists of two blocked conditions: tone decision and semantic decision (9,13). In the tone decision, subjects hear brief sequences of four to seven 500- and 750-Hz tones every 3.75 seconds and respond with the non-dominant hand button press for any sequence containing either two 750-Hz tones ("1") or other than two 750-Hz tones ("2"). In the semantic decision, subjects hear spoken English nouns designating animals every 3.75 seconds and respond "1" with a non-dominant hand button press to stimuli that meet two criteria: "native to the United States" and "commonly used by humans." In all other cases, they respond by pressing "2".

Functional MRI scanning and post-processing

The imaging was done with either a 3T Bruker Biospec 30/60 (Bruker Medizintechnik, Karlsruhe, Germany, in the Imaging Research Center at the Cincinnati Children's Hospital Medical Center; N = 24) or a 4T Varian (Oxford Magnet Technology, Oxford, UK, in the Center for Imaging Research at the University of Cincinnati; N = 25) MRI scanners. The activations obtained from the 3T and 4T scanners were compared for differences in the distribution or intensity of the activation patterns. Since none were identified, datasets were combined. A detailed description of the differences between two imaging protocols, the compatibility of the scanners and data collection methods, and the methods for combining neuroimaging data from these 2 scanners have been discussed elsewhere (14,43). Briefly, the 3T Bruker MRI scanner is equipped with an audiovisual system for presentation of task stimuli (SV 4120; Avotech Systems Inc., Jensen Beach, FL, USA). Foam padding and a head restraint were used to control for head movement. The subjects were given a button box for generating measurable responses, as well as to alert the MRI technologist to a problem if necessary. The fMRI scanning was performed in thirty-two 5-mm-thick planes sufficient to cover areas extending superiorly from below the inferior aspect of the cerebellum to the apex of the cerebrum. The EPI pulse sequence parameters were: TR/TE = 3000/38 ms; FOV = 25.6 × 25.6 cm; matrix size = 64 × 64; flip angle = 90°. A high resolution T1-weighted, three-dimensional anatomical scan for anatomical localization of the activation maps was also obtained using a Modified Driven Equilibrium Fourier Transform (MDEFT) protocol with the following parameters: TR = 15 ms; TI = 550 ms; TE = 4.3 ms; FOV = 25.6 × 19.2 × 16.2; flip angle = 20°; spatial resolution = 1 × 1 × 1.5 mm. Similarly, for the 4T Varian scanner, 30 axial planes were imaged for the fMRI procedure and were identified from initial scout images. The Varian fMRI parameters were: TR/TE = 3000/25 ms; FOV = 25.6 × 25.6 cm; matrix size = 64 × 64; slice thickness = 4 mm; flip angle array = 85/180/180/90. The Varian anatomical scan parameters were: TR = 13 ms; TE = 6 ms; FOV = 25.6 × 19.2 × 15.0; flip angle array = 22/90/180 with the voxel size of 1 × 1 × 1 mm.

The fMRI image post-processing was performed using in-house developed software in the IDL software environment (IDL 6.3; Research Systems Inc., Boulder, CO, USA). Geometric distortion due to B0 field inhomogeneity was corrected during reconstruction using a multi-echo reference scan (44). Data were co-registered and motion corrected using a pyramid iterative algorithm (45) and transformed into Talairach reference frame prior to statistical analysis (46).

Statistical analysis

GLM analysis—As previously, individual participant data were analyzed using a general linear model (14). Individual maps were concatenated as input for the subsequent second level random effects analysis. The resulting composite maps were corrected for multiple comparisons via a Monte-Carlo simulation (47).

ICA Decomposition—The group ICA was performed according to methods discussed elsewhere (19,25). These methods are briefly discussed here for the purpose of completeness. Initially, the timecourses of all voxels from each subject were normalized to a percent signal change from the mean before performing a two step data reduction procedure (subject and group wise). The ICA decomposition was based on 25 repeated runs of FastICA algorithm combined with hierarchical agglomerative clustering to estimate the most reliable components (48). All components were detected at least in 20 out of the 25 runs assuring a high degree of reliability. These criteria resulted in 51 components for each subject. The corresponding timecourse of each IC map was Fourier transformed (FT) and the component was then subjected to a group analysis at the on-off task frequency as discussed elsewhere (19,25). This analysis resulted in retaining fourteen components that were deemed “semantic

task-related” based on the above mentioned criteria. However, 6 components were rejected as artifacts (motion related) based upon spatial and temporal characteristics following visual inspection by the investigators (data not shown). Similar steps are part of any data driven technique (such as ICA) where the researcher will have to make certain decisions/selections based on other ancillary information. For each of the 8 remaining components, a one-sample t-test was performed on each of the IC maps on a voxel-wise basis to determine if each voxel value was significantly different from zero across the group.

Above, we have only described the main steps of our ICA analysis method and how it was applied to the current data. Although, ICA is becoming a popular method of fMRI data analysis, it is still not the “standard” approach. There are few variations and extensions of ICA (31,49,50); the method developed by our group is a direct extension of the group ICA methods proposed by Calhoun et. al. (51) and has been discussed in detail in our previous publications (19,22,25,52).

RESULTS

The mean number of correct responses for the semantic decision task was 81 ± 12.0 (range 46 – 96). There were no significant effects of age or gender on task performance. The results of a random effects GLM analysis (nominal $z = 20$, cluster size = 200, corrected $p < 0.001$; Figure 1) detected, consistent with our prior report, only the bilateral IFG, left middle frontal gyrus, medial frontal and superior frontal gyri, bilateral parahippocampal and angular gyri, left superior temporal gyrus, lingual gyrus, posterior cingulate and precuneus (14).

The eight semantic decision task-related group ICA maps were identified as shown in Figure 2. These maps show activation in bilateral cuneus (Figure 2 a); bilateral lingual gyrus (Figure 2 b); bilateral inferior frontal gyrus (figure 2 c); left parahippocampal gyrus, inferior temporal gyrus including lingual and fusiform gyrus, middle temporal gyrus, middle occipital gyrus and cuneus (Figure 2 d); bilateral posterior cingulate and middle temporal gyri (Figure 2 e); bilateral hippocampi and amygdale (Figure 2 f); left inferior frontal gyrus, middle temporal gyrus, angular gyrus, inferior parietal lobule, and supramarginal gyrus (Figure 2 g); and the bilateral anterior cingulate gyri (Figure 2 h). Table 2 contains a summary of the respective activation foci for each of the components included in Figure 2. Coordinates listed for each IC correspond to the center of mass of each separate spatial element of the IC. Figure 3 shows the corresponding average timecourses for the respective IC maps shown in Figure 2. The progression from leading to lagging is clearly visualized. Average IC timecourses of the semantic decision were correlated with the on–off task reference function and had correlation coefficient of $r \geq 0.49$ (Table 3; column 3).

The inter-subject variability and laterality was calculated using methods discussed elsewhere and tabulated in Table 3 (column 4) (19,52). Accordingly, for the semantic decision, the components shown in Figure 2 d and 2 g are strongly left-lateralized; the component in Figure 2 a is slightly right lateralized; the component in Figure 2 b is somewhat left lateralized; the component in Figure 2 f is somewhat left lateralized; the other components are bilateral.

DISCUSSION

Semantic processing sub-serves many important cognitive functions making it ideally suited for exploration of language circuitry (9,13). In general, semantic fluency tasks have been shown to produce highly left lateralized patterns of activation in right and even left-handed individuals (11,53). When examined with GLM, akin to the previous studies, the semantic/ tone decision task has shown left hemispheric lateralization (Figure 1). ICA substantiated

the picture of left-hemispheric lateralization of language maps detected by this fMRI task by identifying two IC maps with strong left-hemisphere lateralization (Figure 2 d and 2 g). However, ICA also identified a more complicated language distribution pattern by identifying right-hemispheric and bilateral network components dissimilar to the results of the above model-based method. The overall left-hemispheric lateralization of the semantic decision process detected using the hypothesis driven methods appears to be driven by the 2 d and 2 g components and may be too simplistic when compared to the pattern of an elaborate network revealed by implemented in this study ICA. In addition to detecting the same language nodes as GLM, ICA was able to separate out more distinct and independent components forming the basis for the proposed hierarchical cognitive model for semantic decision tasks (Figure 4) that provides basis for examining the effects of left and right hemispheric epilepsy on semantic processing (16). In the companion manuscript, we test the hypothesis that ICA would reveal additional effects of (or differences between) right- or left-hemispheric epilepsy on the language network (including the effects on the temporal structure of the network) that have not been previously seen with standard methods of data analysis including GLM.

The advantage of spatial ICA is its ability to identify functionally connected regions subserving complex cognitive functions (54). Active cortical regions in the same IC map imply similar temporal behavior while the contribution of each individual cortical region varies depending on the cognitive function it sub-serves. Therefore, if a given cognitive task specifically recruits one brain region then ICA will separate out a component containing only that region. Information provided by other model-driven methods can be used to overcome inherent problems in data driven methods such as ICA. In particular, information provided by GLM and DTI could be used to corroborate or to strengthen the interpretation of the ICA analysis findings. Furthermore, information provided by interregional correlations can also be used to reveal brain connectivity to help interpret ICA results (55). In addition, the information about the relationship between speech monitoring and speech production and/or comprehension can also be used as knowledge base when proposing cognitive models for brain functions (56). Specifically, for the current semantic decision task, we were able to incorporate in the model the observed brain activation in the inferior parietal lobule (Geschwind's territory) that is related to the discrimination between semantic components with written/auditory item presentation (57). The advantages of ICA have also been highlighted by Tie et al. where they specifically investigated whether ICA is, in fact, capable of reducing the type II error as well as to generate more language-specific networks (31). These authors concluded that ICA is capable of identifying more activated voxels in the putative language areas and is capable of isolating signals from other sources into different components. Compared with GLM, ICA identified more activated voxels in the putative language areas, and signals from other sources were isolated into different components.

As pointed out by Binder et. al., mapping of speech comprehension using fMRI differs dramatically in pattern, extent, and lateralization of activation when investigated with GLM methods (10). Additionally, these authors revealed that identification of the semantic network requires an active, nonlinguistic task as a control condition implying a reliance of uncontrolled attentional resources for semantic processing demands. Another study showed that the risk of erroneously associating a given brain activity to a particular cognitive function is extremely high in neuroimaging research (58). One possible approach to address such concerns is to consider each brain region's activation (or function) not as isolated module(s) but rather as part of a network-oriented approach. In this sense, ICA, which is a completely data-driven approach, provides useful methodology to test or generate new hypothesis about the behavior of the cognitive network based on fMRI data. As such, the analyses performed here disclosed the functional circuits and the network structure(s)

responsible for semantic decision with a predominantly data-driven methodology and evaluated the biological relevance of this network against the knowledge-base on human language circuitry.

The semantic task in the present investigation requires perceptual analysis of auditorily presented information. Initially, subjects must pay attention to auditorily presented animal names, phonetically encode them into information storage and then attach meaning to them (59). Accessing the meaning of the word is thought to activate verbal encoding, stored semantic representation and mental imagery. The act of accessing the word's meaning has been shown to activate a broader network that is associated with meaning (60,61). The subsequent semantic decision is subserved by reasoning and semantic memory networks and ends in articulation. Finally, during the entire process, attention must be continuously maintained.

Relative to the ICA results reported here, previously developed language models such as the Wernicke-Lichtheim-Geschwind model that describe left lateralized language functions give only a limited view and interpretation of language processing networks in the brain. Previous studies have also suggested network models of language system based on semi-/complete data driven methods (31,49,55–57). Consistent with semantic fluency studies (62–65), our ICA results demonstrate that the semantic network is comprised of not only left-lateralized sub-networks but our results also highlight the importance of bilateral and right-sided sub-networks for language processing. The existence of such networks is not a surprise as several studies have already shown that e.g., right- and left-handed stroke patients exhibit aphasia after right hemispheric lesions (Coppens et al., 2002) or that crossed aphasia can be evoked with direct cortical stimulation in a right-handed brain tumor patient (66). Other examples of crossed language lateralization include patients with epilepsy (67,68) where expressive language functions are lateralized to one hemisphere while the receptive functions are represented by the contralateral cortex. Therefore, extended models of language must be qualified with reference to the type of language task employed and regions of interest examined. With this in mind, functional modularity of each of the IC modules is briefly discussed below.

Semantic decision modules

The IC module shown in Figure 2 a (cuneus) is thought to be related to mental imagery and visual perception. Several studies of visual mental imagery and visual perception have detected activation in the primary visual cortex (69, 70). However, this task-related activation in cuneus implies the retrieval of stored mental images related to the presented animal names rather than the formation of new mental imagery (70, 71). Overall, this module showed the lowest correlation coefficient with the on-off task reference function and a high degree of inter-subject variability. Unlike the other seven IC components, this is the only somewhat right-lateralized ($LI = -0.14$) component of the semantic decision task.

The IC presented in Figure 2 b shows bilateral symmetric activation in lingual and fusiform gyri implicated in mental imagery processes (69, 70). While one study posited that the left hemispheric activation is more inline with generation of new mental imagery, the bilateral activation of the lingual gyri has been implicated in more elaborated access to stored mental images (70) which is in agreement with the hypothesized model for the semantic decision task (Figure 4). However, as shown with an object naming task, activation in bilateral posterior inferior temporal lobe has also been implicated in semantic representation (72–74) and that the semantic knowledge can be modified through experience (75). In addition, semantic representations have been proposed to emerge from correlations between visual representation of objects (fusiform gyrus) and their verbal descriptions (superior temporal gyrus) using parallel processing mechanisms (76). Thus, in our model we hypothesize that

the lingual and fusiform gyri may be involved in combining verbal and visual information into semantic representations.

The IC map 2 c shows bilateral and symmetric activation in inferior frontal gyri (BA 47) located anterior and ventrally to the classical Broca's area (BA 44/45) and its right-hemispheric homologue. In this study, we hypothesize that this IC is the decision making module based on semantic retrieval, selection and reasoning. Left inferior frontal cortex (BA 47) has previously been implicated in more effortful retrieval or greater selection demands associated with semantic/syntactic processing while the dorsal-posterior (BA 44/45) regions are implicated more in phonological processing (77–80). In addition, an ERP study has shown that activation in bilateral inferior frontal gyrus (BA 47) plays a prominent role in syntactic language and music processing (81) implying a role in processing fine-structured stimuli that evolve over time (82).

The strongly left-lateralized IC shown in Figure 2 d reveals activation in parahippocampal gyrus, inferior temporal gyrus, middle occipital gyrus and cuneus. These areas are thought to be involved in encoding verbal information and generation of new mental imagery. Left medial temporal lobe (including parahippocampal gyrus) has been implicated in encoding auditorily presented animal names; verbal information encoding has been shown to be affected by left but not right temporal lobe epilepsy (12). This module also encompasses activation in the left inferior temporal gyrus, the middle occipital gyrus and the cuneus which is implicated in generation of new mental imagery (see above – IC 2 a). In support of this, several studies of mental image generation with verbal input have shown left-lateralized activation including the parahippocampal gyrus, the inferior temporal gyrus, the middle occipital gyrus and the cuneus (69, 70, 83, 84).

The IC map shown in Figure 2 e shows activation in posterior cingulate cortex and precuneus known to be pivotal for conscious information processing (85). Posterior cingulate and precuneus have hard-wired direct connections to frontal, parietal and temporal cortex; these areas sub-serve visual imagery, spatial attention, episodic memory retrieval, self-processing and consciousness (86). In addition, this area has shown activation during the deductive reasoning process (87). Finally, the activation in middle temporal gyrus has been implicated in processing of abstract concepts while the activation in precuneus has been implicated in processing of concrete concepts (88). Thus, we presume that this module processes both the concrete and the abstract concepts subserving reasoning associated with the semantic decision.

Bilateral activation in amygdala and hippocampi is shown in IC map 2 f (Figure 2 f). This area is presumed to be engaged in encoding and accessing previously stored semantic representations. Medial temporal lobe (MTL) has shown activation during associative encoding processes (89, 90) and encoding of visually presented information (91). In addition, synchronization of theta activities of amygdala and hippocampus have been reported to relate to fear memory retrieval in mice experiments (92). Finally, Greenberg et al. also found co-activation of bilateral amygdala and bilateral anterior hippocampi during the semantic memory retrieval process (93). The results of previous studies are in line with our hypothesis that MTL subserves access to verbally presented semantic representations.

The IC map 2 g shows activation in traditional language-related brain areas including Broca's and Wernicke's as suggested by the Wernicke-Geschwind model (7). Further, as expected, this component has the highest left lateralization index. Wernicke's and Broca's areas are known to be connected bi-directionally through the arcuate fasciculus and/or the cortico-subcortico-cortical pathways (94). In addition, recent tractography (DTI) studies confirmed anatomical connectivity between Broca's area, Geschwind's territory and

Wernicke's area through direct as well as indirect pathways (35,95). We hypothesize, that this IC component, which shows functional connectivity between these three territories subserves language comprehension, syntactic processing and speech production. In addition, this component revealed the lowest inter-subject variability and highest correlation with the on-off task reference function. This component overlaps significantly with and shares its strong left lateralization and semantic task correlation with a similar left-hemisphere network identified using ICA for analysis of fMRI data from a verb generation task (96). We postulate that this IC map is the dominant part of the network that subserves semantic decision task.

In general, Broca's area can be linked to syntactic processing, though it has been specifically linked to syntactic working memory during sentence comprehension (97). The left inferior frontal gyrus (LIFG) can be a candidate for unification processes which combine information retrieved from semantic, syntactic and phonological processing (98). The co-activation of parahippocampal and middle temporal gyri with posterior parietal cortex (angular gyrus, inferior parietal lobule and supramarginal gyrus) suggests a similar unification process by the LIFG for this task. Gerstmann syndrome that presents as finger agnosia, right-left disorientation, agraphia and acalculia has been observed in many cases with lesions in angular gyrus (99,100). Difficulties in semantic access similar to dyslexic patients have been observed in patients with lesions in angular gyrus implying a role for angular gyrus in semantic processing (101). Thus, it is reasonable to assume that the angular gyrus would generally be involved in semantic processing more than in specific cognitive abilities such as reading (99). In addition, the left angular gyrus has been shown to subserve semantic processes based on functional imaging studies (77,102). Similarly, the left supramarginal gyrus has been shown to be specifically engaged in the detection of changes in phonological units (103). The posterior superior temporal gyrus (BA 39/22) has been known to be the center of language comprehension (5,104). The role of this area can be divided into mimicry of sounds and representation of phonetic sequences; both functions are central to the acquisition of long-term memories of novel words (105). Furthermore, based on neuroimaging studies, the inferior frontal cortex around Broca's area has been suggested to act as a phonological rehearsal system connecting to the phonological storage system in the posterior parietal cortex (106–109) as part of the working memory module (110).

The maintenance of attention is necessary for the correct performance of the task. Anterior cingulate cortex in IC map h (Figure 2 h) has been known to sub-serve general attentional control as part of the anterior attentional network (111). A recent fMRI study has shown robust activation in anterior cingulate when processing 'conflicting' trials implying its further role in an executive attentional network (112).

To summarize the discussion on semantic decision modules, the eight task-related independent components are hypothesized to support verbal encoding, semantic decision or attentional demands as shown in Figure 4. Further, this figure shows the hypothesized connections between the IC modules forming the theoretical cognitive basis for the semantic decision task based on an expanded version of Wernicke-Geschwind model. Accordingly, IC maps shown in Figures 2 a, b, and d constitute verbal encoding module. The IC maps shown in Figures 2 c, e, f, and g constitute the semantic decision module. We have adopted a theory-driven focus to guide the interpretation of our results and effectively circumvented the inherent drawbacks of data driven techniques. Based on the proposed theoretical model for this task, the semantic decision modules handle the information retrieval/selection and reasoning as well as attentional demands deemed necessary for semantic decision.

LIMITATIONS

ICA is a data-driven method capable of identifying spatially independent networks subserving specific cognitive functions as part of the semantic/tonic decision task. We inferred each network's modularity and hierarchical order based on existing knowledge and available literature. However, one can also establish the functional modularity of each network based on correlation analysis provided relevant neuropsychological data are available. Furthermore, to compensate some of these drawbacks, ICA can be combined with more sophisticated network analysis methods such as structural equation modeling (SEM) (24,113), path analysis (114,115) or Granger causality (49,116) to resolve unanswered questions regarding causal structure in the semantic decision task. Further, ICA is not completely immune to movement related effects, although it captures some of the motion artifacts as separate IC maps in the group ICA analysis. Nevertheless, individual variability must be fully characterized even for ICA methods to overcome inherent sensitivity issues of fMRI to subject motion. Finally, the network behavior (IC maps) can be affected by differences in individual education level, handedness, age and sex. Although we partially addressed this issue by calculating the inter-subject variability, a more detailed analysis that is beyond the scope of this work could shed more insight on the network behavior at a finer level which can be compared and contrasted to the same networks in subjects with certain diseases, e.g., epilepsy.

CONCLUSION

The findings of the current ICA study are compatible with previously published GLM results of the same task in terms of detected brain regions. However, ICA detected additional brain regions involved in semantic processing not detected in the standard GLM analyses (23). Unlike the standard GLM analyses, ICA provides both the spatial and temporal information laying the foundation for a comprehensive network analysis subserving semantic decision task. The analyses and results described here highlight the additional information gained when analyzing cognitive functions in terms of underlying network structures and demonstrate that the semantic network comprises the left-, right-, and bilateral subnets. More importantly, it highlights the significance of bilateral and right-sided sub-networks in language processing as previously suggested in crossed aphasia patient with right-handedness (117). The most significant part of this network is the left-lateralized component that includes the Broca's and Wernicke's areas (Figure 2 g).

Research highlights

We establish cognitive model for semantic decision using fMRI and independent component analysis.

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Figure 1.

Results from a random effects GLM analysis of 49 healthy subjects where semantic decision was contrasted with tone decision (nominal $z = 4$, cluster size = 100, corrected $p < 0.001$). Slice range: $Z = -20$ to $+55$ mm (Talairach coordinates). All images are in radiologic orientation (left in the brain is right on the picture).

Figure 2.

Eight task-related group independent component maps found for the group of 49 healthy subjects performing semantic decision. Slice range: $Z = -25$ to $+35$ mm (left upper to right lower; Talairach coordinates). Images are in radiologic orientation (left on the picture is right in the brain).

Figure 3.
Associated timecourses for the independent component maps of semantic decision shown in Figure 2. Horizontal axis is time and the vertical axis is intensity (pseudo).

Figure 4.

Hypothesized cognitive model for semantic decision based on group ICA maps shown in Figure 2. The proposed model consists of four modules: 1) verbal encoding and mental imagery module; 2) semantic decision module; 3) Wernicke-Geschwind module (for working memory and output); 4) general attentional module.

Table 1

Demographic characteristics of the enrolled subjects

Age in years		23–30	31–40	41–50	51–59	Subtotal	Total	Mean age		
Sex	M	7	10	6	5	21	49	39.3±12.4		
	F	12	5	3	8	28				
Handedness	Right	47								
	Left	2								

Table 2

Anatomical and Brodmann's area locations and the Talairach coordinates of the activation foci detected by independent component analysis foci for the independent components displayed in Figure 2.

Task condition	ICA component	Anatomical Area	L/R	Brodmann Area	Coordinates		
					x	y	z
Semantic task (Figure 2)	a	Cuneus	L	18	-2	-73	15
			R	18	2	-73	15
	b	Lingual gyrus	L	23	6	-81	-1
			R	18	-6	-81	-1
	c	Inferior frontal gyrus	L	47	-34	19	9
			R	47	34	15	-9
	d	Parahippocampal gyrus	L	35	-22	-33	-9
		Lingual gyrus	L	30/19	-18	-45	-1
		Fusiform gyrus	L	19/18	-22	-65	-13
		Middle temporal gyrus	L	39	-34	-61	11
		Middle occipital gyrus	L	19	-30	-73	11
		Cuneus	L	17/18	-14	-77	7
	e	Posterior cingulate	L	29/30	-10	-49	11
			R	29/30	6	-49	11
		Middle temporal gyrus	L	37/21	-46	-57	7
			R	37/21	38	-53	7
	f	Hippocampus	L		-26	-21	-13
			R		22	-25	-13
		Amygdala	L		-26	-9	-17
			R		22	-9	-17
	g	Anterior cingulate gyrus	L	32	-14	43	15
		Inferior frontal gyrus	L	44/45	-42	23	7
		Superior temporal gyrus	L	39/22	-46	-53	11

Task condition	ICA component	Anatomical Area	L/R	Brodmann Area	Coordinates		
					x	y	z
		Angular gyrus/Inferior parietal lobule/supramarginal gyrus	L	39/40	-37	-51	21
		PHG	L	36/38	-14	-33	-9
		Thalamus	L		-14	-21	7
	h	Anterior cingulate gyrus	L	32/24	-2	35	11
			R	32/24	10	31	11

Table 3

Correlation coefficients (column 3) with the task reference function associated with the time courses displayed in Figure 3 for each component listed in Table 2. Column four shows the inter-subject variability for each of the ICA time courses shown in Figure 3. Column five shows the lateralization indices (LIs) computed for each of the components in Figure 2.

Task	Component	Correlation with task	Variability	LI
Semantic	Figure 2a	0.49	0.960110	-0.14
	Figure 2b	0.49	0.945593	0.15
	Figure 2c	0.48	0.959189	-0.01
	Figure 2d	0.50	0.951606	0.91
	Figure 2e	0.76	0.896192	0.10
	Figure 2f	0.63	0.947720	-0.06
	Figure 2g	0.88	0.820854	1.00
	Figure 2h	0.73	0.966868	0.03