Efficiency of semantic processing measured by N400m and its correlation with anisotropy of the Inferior Longitudinal Fasciculus

Jiwon Shin

Integrated Program in Neuroscience
Faculty of Medicine
McGill University
Montreal, Quebec, Canada

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Table of Contents

Table of Contents ................................................................. 3
Abstract ................................................................................. 5
Résumé ...................................................................................... 6
Acknowledgements ................................................................. 7
Preface & Contribution of Authors ............................................. 8
Introduction and Statement of the Problem ............................... 9
Background Information .......................................................... 11
  Function and Structure ......................................................... 11
  Inferior Longitudinal Fasciculus (ILF) ................................. 12
  Visual Semantic Processing in the Ventral Language Stream .... 15
  Magnetoencephalography (MEG) .......................................... 18
  N400m ................................................................................. 19
  Diffusion Tensor Imaging (DTI) ............................................. 22
  Fractional Anisotropy (FA) .................................................. 25
Current Study: Hypothesis & Specific Aims .............................. 27
Methods ................................................................................... 28
  Ethical Aspects ................................................................. 28
  Subjects .............................................................................. 28
  MEG Data Acquisition ...................................................... 29
  MEG Analysis .................................................................... 31
  MRI Data Acquisition ....................................................... 33
  DTI Analysis ..................................................................... 34
Abstract

The inferior longitudinal fasciculus (ILF) is a white matter tract that connects the occipital and the temporal lobes. Due to its location, a possible role in visual processing and language comprehension has been attributed to the ILF. The present study aims to investigate the existence and degree of an effect of the ILF’s structural organization on visual semantic processing. We hypothesized that the efficiency of visual semantic processing positively correlates with the degree of anisotropy of the ILF. We studied 10 healthy right-handed subjects. We extracted N400m from magnetoencephalography (MEG) signals during a semantic decision task and determined fractional anisotropy (FA) of the ILF using diffusion tensor imaging (DTI). By comparing inter-individual differences in N400m and FA, we found that FA of the left ILF negatively correlated with the N400m latency, which suggests that high ILF anisotropy is associated with more efficient semantic processing. Our findings provide supporting evidence for a role of the ILF in language comprehension.
Résumé

Le faisceau longitudinal inférieur est une fibre nerveuse de la substance blanche qui connecte les lobes occipital et temporal. En raison de son emplacement, un rôle possible dans le traitement visuel et la compréhension du langage, a été attribué au faisceau longitudinal inférieur. Cette étude a pour but d'examiner l'existence et le degré de l'effet de l'organisation structurelle du faisceau longitudinal inférieur sur le traitement visuel sémantique. Nous émettons l'hypothèse que l'efficacité du traitement visuel sémantique est corrélée positivement avec le degré d'anisotropie du faisceau longitudinal inférieur. Nous avons étudié 10 sujets sains en santé. Nous avons extrait N400m de signaux de la magnétoencéphalographie pendant une tâche de décision sémantique et avons déterminé l'anisotropie fractionnelle du faisceau longitudinal inférieur en utilisant l'imagerie du tenseur de diffusion. En comparant les différences inter-individuelles dans N400m et l'anisotropie fractionnelle, nous avons découvert que l'anisotropie fractionnelle du faisceau longitudinal inférieur dans l'hémisphère gauche corrélée négativement avec la latence de N400m, suggérant que l'anisotropie élevée du faisceau longitudinal inférieur est associée avec un traitement sémantique plus efficace. Nos résultats fournissent des preuves à l'appui d'un rôle du faisceau longitudinal inférieur dans la compréhension du langage.
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Preface & Contribution of Authors

The research project presented in this thesis was conducted at the University of Montreal (MEG data acquisition), at the Montreal Neurological Institute (DTI data acquisition and MEG data analysis), and at the Translational Neuroimaging Laboratory, McGill Center for Studies in Aging at Douglas Research Institute (DTI data analysis).

**Experimental concept and design:** Jiwon Shin and Eliane Kobayashi

**MEG mapping design:** Eliane Kobayashi, Pierre Jolicoeur, Denise Klein, and Christophe Grova

**MEG and DTI data acquisition:** Jiwon Shin

**MEG analytical tools:** Christophe Grova and Rasheda Chowdhury

**MEG data analysis:** Jiwon Shin

**DTI data analysis:** Jiwon Shin and Jared Rowley

**Statistical tools:** Christophe Grova

**Statistical analysis:** Jiwon Shin

**Drafting manuscript:** Jiwon Shin

**Manuscript supervision:** Eliane Kobayashi, Denise Klein, and Christophe Grova
Introduction and Statement of the Problem

The inferior longitudinal fasciculus (ILF) is a major ventral associative bundle that connects the occipital and the temporal lobes. Due to its location, researchers have proposed that the ILF plays a role in visual processing and language comprehension (Mishkin et al., 1983, Catani et al., 2003, Catani and Thiebaut de Schotten, 2008). Several recent studies have supported its role in such functions by assessing its anisotropy through neuroimaging (Wong et al., 2011, Ortibus et al., 2012, Taddei et al., 2012). Anisotropy is a property of a white matter tract that infers the degree of structural organization and the efficiency of information transfer (Johansen-Berg, 2010) – the efficiency of information transfer describes both time and effort involved in cognitive processing. However, our knowledge of specific roles played by the ILF in language comprehension is still limited.

Semantic processing is part of language comprehension, which assesses the meaning of a presented word and associates it to other words with similar meanings (Quillian, 1967). A recent study has shown that anisotropy of the ILF relates to semantic processing of auditory language function (Wong et al., 2011). Although evidences of the ILF’s role in visual processing and language comprehension have emerged, no study has specifically confirmed its role in visual semantic processing or explored the degree of this association.

Since brain functions are strongly related with its anatomical connectivity patterns (Passingham et al., 2002), changes in the ILF’s structure may affect functions served through its fibers, such as language comprehension. Determining
how the ILF affects visual semantic processing can provide more accurate knowledge of normal language functions, which may build a basis for assessing the diseased brain and also for understanding functional impairments.

In this study, we aim to investigate the existence and degree of the ILF’s effect on visual semantic processing. We hypothesize that the efficiency of visual semantic processing positively correlates with the degree of anisotropy of the ILF. We recorded brain activity during a semantic decision task using magnetoencephalography (MEG) and measured the structural organization of the ILF using magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) acquisition.
Background Information

Function and Structure

Function is strongly related to anatomical brain organization (Passingham et al., 2002). Advances in functional neuroimaging techniques have allowed us to better understand how language is distributed in the brain. Despite a substantial increase in research of the organization of language at the cortical level (Vigneau et al., 2006), we still do not know much about the subcortical structure connecting the cortical language network. Function of a brain region relies on information available to it via its incoming connections, and it influences other brain regions via its outgoing connections. Therefore, it is important to examine white matter pathways to study how language function and structure are related. Because the white matter tracts connect and transmit information between brain areas in a functional network, it has been suggested that individual differences in white matter tract integrity may reflect individual ability and efficiency of cognitive functions (Johansen-Berg, 2010). This can be easily noticed in neurological patients with white matter degradation and reduced functions. For example, in brains of epileptic patients, language disturbance is often observed accompanied by a change in the integrity of uncinate and arcuate fasciculi (Rodrigo et al., 2008, Kim et al., 2011).

Many researchers have examined this relationship between function and its underlying structure in language studies. For example, DTI and postmortem studies have demonstrated a hemispheric asymmetry of white matter tracts, such
as the arcuate fasciculus, related to hemispheric language dominance (Geschwind and Levitsky, 1968, Rodrigo et al., 2008, Ellmore et al., 2010, Thiebaut de Schotten et al., 2011). Some studies have also combined functional neuroimaging and DTI tractography to investigate how certain white matter connections influence language functions (Powell et al., 2006, Rodrigo et al., 2008, Ellmore et al., 2010, Wandell, 2011). These studies have demonstrated that the success of performance, time and amplitude of brain activities in language task (such as speech production and reading) positively correlates with the anisotropy of the white matter tract that subserves the function.

**Inferior Longitudinal Fasciculus (ILF)**

Brain white matter is composed of bundles or fascicles of axons that connect different grey matter areas. White matter bundles transferring signals within the brain are categorized into projection fibers connecting the cortex and the rest of central nervous system (lower parts of the brain and the spinal cord), commissural fibers connecting two hemispheres, and associative fibers connecting different lobes in the same hemisphere.

The ILF is a ventral associative bundle that links and transfers information between the occipital and the temporal lobes. It is located inferiorly and laterally to the temporal horn of the lateral ventricle (Catani et al., 2003), and is one of the white matter connections in the ventral language stream involved in semantic processing (Duffau et al., 2008, Wong et al., 2011). It was first described in 1819
by the German neuroanatomist K.F. Burdach using postmortem dissection (Burdach, 1819, Polyak and Klüver, 1957). Since the initial discovery, scientists have largely disputed the integrity of ILF; some researchers have viewed the ILF as part of a visual projection system and some have even denied its existence using autoradiography and postmortem dissection (Flechsig, 1896, Niessl-Mayendorf, 1903, Putnam, 1926, Tusa and Ungerleider, 1985). However, more recent investigations have repeatedly confirmed its existence, with anatomical definition distinct from a visual projection system in non-human primates and humans through postmortem dissection, DTI and electric stimulation (Ludwig and Klingler, 1956, Mori et al., 2002, Catani et al., 2003, Mandonnet et al., 2007, Schmahmann et al., 2007, Catani and Thiebaut de Schotten, 2008, Thiebaut de Schotten et al., 2011). These studies have also confirmed that the ILF begins in the occipital lobe and terminates in the anterior temporal lobe.

Due to its location, researchers have speculated that the ILF allows fast access of visual information (Mishkin et al., 1983, Catani et al., 2003, Catani and Thiebaut de Schotten, 2008). From recent findings, we now know more specifically that the ILF plays a role in object recognition (Ortibus et al., 2012), face processing (Taddei et al., 2012) and visual semantic memory (Ross, 1980). These functions involve extracting the meaning of visual stimuli, and they are related to language comprehension as language comprehension also involves analyzing the meaning of presented language stimuli. Therefore, we can understand that the ILF generally provides links to high-level semantic processing taking place in the temporal areas (Vigneau et al., 2006, Hickok and Poeppel,
The ILF degeneration is observed with the onset of post-surgical alexia, and it has been proposed that the ILF transfers visual inputs to the brain area involved in letter-string analysis (Epelbaum et al., 2008).

The ILF’s role in language comprehension has also been demonstrated using DTI and electric stimulation (Mandonnet et al., 2007, Saur et al., 2008, Wong et al., 2011). Mandonnet and colleagues have demonstrated that the ILF indirectly affects the network involved in language semantics, using intraoperative electric stimulation (Mandonnet et al., 2007). Saur and colleagues, using functional MRI (fMRI) and DTI, have demonstrated the ILF as part of a language comprehension network that processes the meaning of a linguistic sound (Saur et al., 2008). Wong and colleagues have followed this study and have investigated more specific roles of the ventral language pathway in language comprehension using DTI (Wong et al., 2011). They have examined semantic processing by using a sound-to-word learning paradigm in which subjects learned to use a foreign phonetic contrast for signaling word meaning. The success in this task positively correlates with the white matter anisotropy of the ventral language pathway. Wong’s group has suggested that this language comprehension function of the ventral language stream is mainly subserved by the ILF. Also, a study involving a reading task showed anatomical changes of the ILF, including anisotropy, in semantic dementia and proposed its involvement in semantic and lexical processes (Agosta et al., 2010). Although evidences of the ILF’s role in visual processing and language comprehension have emerged, no study has
confirmed its role in visual semantic processing and explored the degree of the association.

**Visual Semantic Processing in the Ventral Language Stream**

Current views on language distribution within the brain suggest that language is organized into ‘dorsal’ and ‘ventral’ streams. The ‘dorsal’ stream projects toward the inferior parietal and posterior frontal regions and it is associated with language articulation and speech perception. The ‘ventral’ stream projects toward the middle and inferior temporal cortices and it is associated with language comprehension (Hickok and Poeppel, 2004, Vigneau et al., 2006, Hickok and Poeppel, 2007, Saur et al., 2008, Wong et al., 2011).

In linguistic theory, language comprehension is divided into two distinct functional subsystems: syntactic and lexical (Chomsky, 1986, Ullman, 1997, Pinker, 2000, Ullman, 2001). The syntactic system (a rule-based grammatical system) is located in the left anterior temporal regions, whereas the lexical system (a catalogue of words) is located in the left middle temporal regions. Semantic processing, part of the lexical processes, generally refers to a cognitive stimulus processing in which the meaning of the stimulus is analyzed. It requires accessing semantic memory, the system of meanings, understandings and concepts (Martin, 2001). Semantic memory includes our memory of word meanings. Thus, semantic processing (or lexical-semantic processing) can be viewed as a process that
evaluates the meaning of a presented word and relates it to other words with similar meanings (Quillian, 1967, Demonet et al., 1992).

In visual language comprehension, semantic processing is observed during silent reading. Silent reading consists of a series of simple steps (i.e., seeing, recognizing, and understanding) that have been studied with functional neuroimaging and neurophysiology techniques such as electroencephalography (EEG), fMRI and MEG (Kutas, 1993, Billingsley-Marshall et al., 2007, Service et al., 2007, Lau et al., 2009). When a word is visually presented, basic visual features are processed bilaterally in the occipital lobes at about 100 ms. This process does not differentiate between letter strings and other visual inputs (Tarkiainen et al., 1999, Pammer et al., 2004). At 170 ms post-stimulus, letter-string analysis takes place in the left occipitotemporal cortex (Tarkiainen et al., 1999, Pammer et al., 2004, Stockall et al., 2004, Epelbaum et al., 2008, Wandell, 2011). This response to pre-lexical visual processing is specific to letter strings and, therefore, does not differentiate between words and non-words; the response is insensitive to lexicality either in amplitude or in latency (Tarkiainen et al., 1999, Pylkkänen et al., 2002). The visual semantic processing extracts the meaning of a presented word. The evoked responses for this processing are found at about 400ms after the visual stimulus presentation in the left superior and middle temporal gyri (Kutas and Hillyard, 1980, Helenius et al., 1998, Halgren et al., 2002, Billingsley-Marshall et al., 2007, Service et al., 2007, Lau et al., 2008).
The superior and middle temporal gyri, in which visual semantic processing takes place, are also activated during language comprehension tasks regardless of modality of the presented stimulus (auditory or visual) and experimental tasks (Demonet et al., 1992, Helenius et al., 1998, Billingsley-Marshall et al., 2007, Service et al., 2007, Lau et al., 2009). This suggests that although the recognition of presented information may take place in different brain areas depending on whether information is auditory or visual, the information is transferred to the same brain region (i.e., the superior and middle temporal gyri) for analyzing the meaning of presented stimuli. Thus, it may be reasonable to suppose that the ILF, which plays a role in auditory semantic processing, also participates when stimuli are visually presented (Wong et al., 2011). However, because this processing takes place in the same region, we cannot assume the same for the pathways connecting the brain areas, and that the ILF will play the same role when visual stimuli are involved; the nature of the associated fiber tracts may be different considering that the initial information processing takes place in different brain areas: visual stimulus in the visual cortex (Pylkkänen and Marantz, 2003, Salmelin, 2007, Lau et al., 2009) and auditory stimulus in the primary auditory cortex (Demonet et al., 1992, Bentin et al., 1993). In this study, we evaluate whether the ILF’s anisotropy is associated with the efficiency of visual semantic processing.
Magnetoencephalography (MEG)

MEG non-invasively measures magnetic fields produced by the brain. It allows fast tracking of brain activations at millisecond time resolution and 2-3 millimeters cortical spatial discrimination (Hämäläinen et al., 1993, Lounasmaa et al., 1996). Indeed, the fine temporal and spatial resolutions of MEG are major advantages over other mapping techniques. It has higher spatial resolution than EEG, whose signal is more easily distorted by the skull and scalp (Cohen and Cuffin, 1983). MEG has higher temporal resolution than fMRI, which relies on hemodynamic responses that occur at several seconds time window (Kim et al., 1997).

MEG allows faster stimuli presentation and discrimination of their individual brain responses. These qualities are especially important for tracking the time course of language processing through evoked field response which happens within a few hundreds of milliseconds (Pylkkänen and Marantz, 2003). For example, when silent reading is performed with MEG, different simple brain processes can be identified as event related fields (ERF): N100m in bilateral occipital lobes for visual stimulus recognition, M170 in the left occipitotemporal cortex for letter-string analysis, and N400m in the left superior and middle temporal gyri for semantic processing. In sentence presentation, each word elicits a N400 response (Kutas and Van Petten, 1990). In our study we aim to identify N400m and to measure its amplitude and latency as an index for visual semantic processing.
**N400m**

The ERF N400m (magnetic N400) is originally derived from EEG, identified as a negative deflection (N) that peaks around 400ms (400) after stimulus presentation (Kutas and Hillyard, 1980). Researchers have associated N400m with processing of any potentially meaningful stimuli such as faces, pictures and words (Kutas and Hillyard, 1980, Eimer, 2000, Federmeier and Kutas, 2001). Although N400m has been known to be evoked with other meaningful stimuli, it has been mostly investigated as a lexical response evoked by words in cognitive studies. It has been proposed that the brain process underlying the N400m response reflects the difficulty to access stored semantic memory that contains the meanings of words (Van Petten, 2006). Thus, it has been identified as an index of lexical-semantic processing, which is associated with lexical retrieval and language comprehension (Kutas and Hillyard, 1980, Lau et al., 2009, Kutas and Federmeier, 2011). Because N400m can be elicited by experimental paradigms involving simple semantic priming (Kutas, 1993, Lau et al., 2009), it has played a major role in cognitive studies involved in mapping language functions.

The amplitude of N400m is sensitive to many factors, including semantic priming. Semantic priming is a phenomenon in which recognition of a target word (example, “DOG”) is facilitated when it is preceded by a semantically related prime word (example, “ANIMAL”) as compared to an unrelated prime word.

Semantic processing involves pre-lexically developed expectancies and post-lexical semantic matching (Neely et al., 1989). Expectancies after recognition of the prime word are developed, increasing access to semantically related words, which in turn decreases the processing difficulty. Since N400m reflects the ease of access (Kutas and Federmeier, 2000, Federmeier, 2007), in the semantic priming paradigm, the amplitude is reduced when target words are preceded by semantically related primes or by the same word (Huff et al., 1988, Holcomb, 1993, Kiefer and Spitzer, 2000). Thus, the amplitude of N400m negatively reflects facilitated access of lexical information, which means that a reduction in amplitude reflects increased efficiency in information transfer (Lau et al., 2009). With this rationale, we can modulate the amplitude of N400m in lexical decision tasks by using priming, a “baseline condition” with an easy lexical access, and “comparison conditions” with a difficult lexical access. N400m amplitude variations are also observed in individuals with different processing abilities (Taylor et al., 2011, van den Brink et al., 2012). For example, age-related difficulties in language processing have been reflected by reduced amplitude (Taylor et al., 2011). The differences in amplitude can not only be observed at the group level, but can also be significant enough to be observed at the subject-level, associated with inter-individual differences in cognitive processing ability (van den Brink et al., 2012).

The time it takes for N400m to be evoked (i.e., its latency) is closely related to the speed at which the meaning of a word can be activated. (Helenius et al., 1998), and is often studied as an index of cognitive processing ability and
efficiency. The latency of N400m, along with the amplitude, is higher in aphasic patients as compared to healthy subjects (Kitade et al., 1999). The fact that N400m latency reflects processing efficiency is actually a simpler and easier concept to grasp; the faster cognitive brain processing takes place, the more efficiently the information is transferred from the initial processing of a presented stimulus. In our study, we considered the amplitude and the latency of the N400m response as indices for efficiency in semantic processing. We aimed to evaluate whether differences in latency and amplitude may be associated with the structural organization of the ILF tract.

N400m also serves as an index for language lateralization, as it reliably lateralizes and localizes in the left superior and middle gyri in right-handed subjects (Helenius et al., 1998, Halgren et al., 2002, Billingsley-Marshall et al., 2007, Service et al., 2007, Lau et al., 2008). This lateralization begins from the letter-string analysis around 170ms in the left occipitotemporal cortex and continues to N400m response within a 300-500ms time window (Salmelin, 2007, Service et al., 2007, Maurer et al., 2008, Lau et al., 2009). In accordance with the functional lateralization, DTI studies show leftward asymmetry of the ILF determined by the degree of anisotropy; the anisotropy of the ILF in the left hemisphere is significantly greater than that of the right hemisphere (Verhoeven et al., 2010, Thiebaut de Schotten et al., 2011, Menjot de Champfleur et al., 2012). Both Thiebaut de Schotten’s group and Menjot de Champfleur’s group have determined the structural lateralization of the ILF to be the greatest compared to other association tracts in the brain, such as arcuate fasciculus and uncinate.
fasciculus, with lateralization index, \((\text{left} - \text{right}) / 0.5 \text{ (left} + \text{right)})\) greater than 0.5 in both studies (Thiebaut de Schotten et al., 2011, Menjot de Champfleur et al., 2012).

**Diffusion Tensor Imaging (DTI)**

EEG, fMRI, and MEG allow the examination of cortical areas involved in language. However, with these techniques alone, we cannot examine which white matter tracts connect language-related brain areas and how they affect performance. Recent studies have combined functional neuroimaging with DTI in order to examine the language functions and the associated subcortical white matter pathways (Catani et al., 2005, Powell et al., 2006, Mandonnet et al., 2007, Rodrigo et al., 2008, Ellmore et al., 2010, Wandell, 2011). In our study, we use MEG and DTI to examine how the ILF plays a role in the visual semantic processing which involves visual recognition in the visual areas, letter-string analysis in the occipitotemporal areas, and semantic processing in superior and middle temporal areas.

There are two techniques used to study white matter connections and their anatomy in human brain: post-mortem fiber dissection and diffusion tensor imaging. Post-mortem fiber dissection allows direct visualization of grey and white matter in the postmortem brain. Being one of the earliest methods used, this technique has played a critical role in advancing the study of human neuroanatomy. However, fiber dissection is limited in its accuracy and reliability.
in differentiating fiber anatomy, because it cannot separate a certain fiber system and is prone to artefacts (Yasargil et al., 2004). Moreover, this technique’s use is only limited to post-mortem brains, which may already involve changes in white matter integrity due to medical conditions or aging. Recently, development in diffusion MRI has enabled an indirect assessment of the organization and integrity of white matter tracts *in vivo*. DTI is a non-invasive MRI technique that measures three-dimensional diffusion properties of water molecules (Mori and Zhang, 2006, Jones, 2008, Behrens and Jbabdi, 2009).

The principle of DTI is based on Brownian motion or diffusion: molecules in a fluid constantly move in random directions based on thermal energy (Brown, 1828). Although it is impossible to determine a single molecule’s movement, it is possible to characterize average displacement of numerous molecules in a period of time. In human bodies, water molecules move differently depending on the underlying microstructure; the presence of microstructures such as cell membranes limits the pathways of water molecules undergoing random motions. We can think of these water molecule movements as different “shapes” of diffusion depending on the type of diffusion medium it is placed in (Beaulieu, 2002, Jones, 2008). When a molecule is in an unrestricted medium, such as a ventricle, it diffuses freely in any direction without preference. This gives a spherical shape of diffusion called isotropic diffusion. On the other hand, when a molecule is in a restricted medium, such as within a white matter fiber, it diffuses with preference in a certain direction. This results in an ellipsoidal shape of diffusion called anisotropic diffusion (Mori and Zhang, 2006). Mathematically
determining anisotropy in each voxel involves calculating tensors using eigensystem. The axes of the diffusion ellipsoid and the directions of diffusion in three dimensional space (x, y, and z) are indicated by eigenvectors (ν1, ν2, ν3). The magnitude of each eigenvector, which is a rate of diffusion in each direction, is indicated by eigenvalues (λ1, λ2, λ3). For example, a preferred direction of diffusion in a voxel is described by the primary eigenvector (ν1) which is associated with the largest eigenvalue (λ1). The diffusion anisotropy, the extracellular property describing the directionality in diffusion, thus allows one to infer how orderly structured the white matter connections are.

Although we have limited knowledge of the neuroanatomical source of anisotropy, studies so far have shown that axonal membranes play a primary role, along with other microstructures such as cell membranes, myelination, axonal packing and axon diameter (Beaulieu and Allen, 1994b, a). All these microstructures affect the efficiency of information transfer through conduction velocity, impulse firing rate, length of the refractory period and the probability of axonal firing (Fields, 2008), which suggests that anisotropy reflects the efficiency of transfer.

Although DTI allows us to reconstruct and visualize white matter fibers in vivo, there are inherent technical limitations. At each voxel, DTI allows information of a single tensor, whereas the anatomical information may be more complicated. DTI cannot distinguish the existence of branching or crossing fibers from fibers of the dominant orientation; it shows the average orientations of white
matter fibers at each voxel (Mori et al., 2002, Wakana et al., 2004). This may result in false positive and false negative reconstruction of white matter tracts. However, several new fiber mapping techniques have developed to improve DTI tractography. For example, High-Angular Resolution Diffusion Imaging (HARDI) and Diffusion Spectrum Imaging (DSI) increase angular resolution by allowing multiple tensor directions. These techniques can account for the problem DTI has with branching or crossing fibers. However, these techniques are not frequently used in white matter studies, because the analysis using these techniques is not widely available. Also, although DTI only allows indirect measurements and replicates some neuroanatomical features with imperfection (Fernandez-Miranda et al., 2012), researchers have proven reliability and consistency between the regenerated white matter tracts and post-mortem data (Thiebaut de Schotten et al., 2011).

**Fractional Anisotropy (FA)**

FA quantifies the degree of anisotropy within each voxel on a scale from 0 to 1 (higher value reflects high alignment of structures along a certain direction) (Pierpaoli and Basser, 1996). Compared to other DTI indices such as mean diffusivity and radial diffusivity, FA better represents white matter directional coherence and organization (Pierpaoli and Basser, 1996, Mori and Zhang, 2006). In addition, FA better correlates with functional lateralization of language than other measurements (Powell et al., 2006, Rodrigo et al., 2008, Thiebaut de
Schotten et al., 2011). However, FA does not take multiple directionality into consideration (Wiegell et al., 2000). Although the integrity of a tract does not change, the introduction of a crossing or branching fiber can significantly reduce local FA value. Due to such limitations, prior anatomical knowledge about the white matter tracts of interest is greatly advised before acquiring and analyzing DTI data.
Current Study: Hypothesis & Specific Aims

In this study, we examined the existence and degree of an effect of the ILF’s integrity (through DTI analysis) on visual semantic processing (assessed through MEG mapping) in right-handed subjects, who we can assume to have left hemisphere language dominance. We consider the mean FA of the ILF obtained from DTI analysis as the structural measure, and the latency and amplitude of N400m obtained from MEG mapping as the functional measure of this network. In addition, we consider that the mean FA of the ILF indirectly reflects the efficiency of information transfer, whereas the latency and amplitude of N400m reflects the facilitation of visual semantic processing (the shorter the latency and the smaller the amplitude, the more facilitated the processing). Using these measures, we aim to investigate if the inter-individual differences in visual semantic processing positively correlate with the anisotropy of the ILF. Our specific hypothesis is:

- N400m latency and amplitude negatively correlate with the mean FA of the ILF in the left hemisphere. Thus, the higher ILF anisotropy is, the more facilitated visual semantic processing is.
Methods

Ethical Aspects

This project has been approved by the Montreal Neurological Institute Research Ethics Board. All participating subjects signed written informed consents for both data acquisition sessions (i.e., MRI and MEG).

Subjects

A total of 19 healthy right-handed fluent English-speaking subjects participated in this study (8 female, age 18-40 years, mean: 26.2±5.8 years). Handedness was determined using the Edinburgh Handedness Inventory. Left-handed subjects were excluded, as they might have atypical language representation (Duffau et al., 2008). All subjects had normal vision or normal vision through corrective lenses. We excluded six subjects from the MEG data analysis after acquisition due to excessive motion (N=2), excessive blinking (N=2), incomplete acquisition due to technical problems (N=1), and improper positioning which interfered with the subject’s vision (N=1). Subsequently, subject selection was done according to the quality of individual N400m signal: a clear peak between 300 ms and 500 ms with the signal-to-noise ratio of 1.5 and above. Thus, this study reports on 10 subjects (5 female, age 18-36 years, mean 25.3±5.9 years). Details of inclusion and exclusion criteria for this study are explained below.
MEG Data Acquisition

MEG recording took place at the University of Montreal using a CTF system (VSM MedTech Ltd, Canada), equipped with 275 axial gradiometers. We recorded MEG signals at 1200Hz sampling rate. We monitored eye movements using an electro-oculogram (EOG), and motion artifacts using electrocardiogram (EKG).

MEG mapping protocol included a lexical-semantic decision task based on semantic categorization. This semantic task is designed for subjects to actively process stimuli at the level of meaning and elicit brain responses associated with visual semantic processing. In our study, subjects were visually presented with 240 prime-target word pairs (example: FLOWER / ROSE) projected on to a screen. Prime and target words produced two equiprobable paradigms: related pairs (example: FLOWER / ROSE) and unrelated pairs (example: FLOWER / SOCCER). The “related” condition was expected to elicit smaller N400m due to greater priming as compared to the “unrelated” condition. The subject had to decide whether or not the target word belonged to the category of the prime word (if the target word was related or unrelated to the prime word).

Each prime word was shown for 1000 ms, followed by a target word, which is presented up to 1000 ms. The subject had to press the appropriate button (according to previously provided instructions) within 1000 ms of target word presentation. Beyond that timing, the response was considered late and the trial was excluded from the analysis. Instruction on which button to press (using either
the left or the right thumb) was given at the beginning of each test blocks in a session. After two blocks, subjects were instructed to reverse the sides of the response. For example, if the first two blocks required subjects to press the left button for “related” pair and right button for “unrelated” pairs, the last two blocks required subjects to press the right button for “related” pairs and the left button for “unrelated” pairs. We introduced this reverse in hand in order to prevent motor response bias that may be caused by subjects’ handedness.

A feedback response was displayed after the subject’s button press or 1000 ms of the target presentation if he/she did not make a button press. The feedback was visually presented as: ‘+’ for correct, ‘-’ for wrong, and ‘l’ for late responses.

The list of items was constructed from a list of 12 highly frequent words in each of 17 different categories (Van Overschelde et al., 2004), which excluded homonyms and compound words. Categories consisted of animals, birds, body parts, carpenter’s tools, clothing, colors, countries, flowers, fruits, furniture, insects and musical instruments. The frequency of appearance of each word was controlled in order to avoid effects of priming on N400m. The more frequently presented a word is, the more primed the brain is to it. This results in less semantic memory searching, thus the less cognitive processing one engages in and the smaller N400m amplitude (Kutas and Federmeier, 2000, Matsumoto et al., 2005, Federmeier, 2007, Lau et al., 2009).
MEG Analysis

We pre-processed MEG signals using Data-Editor software (CTF, VSM MedTech Ltd, Canada). Signals underwent sub-sampling at 600 Hz, third order gradient correction, band-pass filtering (0.3-40 Hz), and removal of epochs containing eye blinks and excessive movements. For each trial, an epoch was segmented and baseline-corrected, containing signals from -200 ms to +700 ms in relation to target word presentation. We excluded wrong and late responses; correct responses were used for generating an average dataset for “related” and “unrelated” conditions. The reason for including only correct responses was to avoid inclusion of non-N400m signals – the brain activity after an incorrect or late response may involve additional cognitive processes such as detecting errors and attempting to correct errors, which elicit additional responses in different brain regions, such as cerebellum, mesial prefrontal cortex and anterior cingulate cortex (Carter et al., 1998, Desmond et al., 1998, Rubia et al., 2003). To exclude responses to visual stimuli not related to N400m, we subtracted signals in the “unrelated” condition average from signals in the “related” condition average. Although the amplitude of N400m are expected to be greater in the “unrelated” condition than in the “related” condition due to priming effect, such amplitude difference are not expected in N100m, the ERF indicating primary visual stimulus recognition, and M170, the ERF indicating letter-string analysis, because N100m and M170 are insensitive to semantic properties of a presented word (Tarkiainen et al., 1999, Wydell et al., 2003, Pammer et al., 2004, Maurer et al., 2008). Since the amplitudes of N100m and M170 do not differ between “unrelated” and
“related” conditions, the subtracted signal was considered to reflect the N400m response only (Figure 1).

Figure 1: MEG signals of brain response to silent reading. a) The colored lines (green – left hemisphere sensors; blue – right hemisphere sensors) represent the signals of “unrelated” condition and the grey lines represent the signals of “related” condition. The amplitudes of N100m and M170 are not significantly different between “unrelated” and “related” conditions. The amplitude of N400m is greater in the “unrelated” condition than the “related” condition.

All subjects included in the study fulfilled the following MEG signal criteria: N400m response in the subtracted signal had to be present in N400m time window of 300ms and 500ms (Service et al., 2007, Lau et al., 2009), with a signal-to-noise ratio of 1.5 and above compared to the baseline – from 200 ms before the stimulus presentation (- 200 ms) to the stimulus presentation (0 ms).
Once N400m response with its peak in the expected time window is identified, we assessed the signal-to-noise ratio using the mean magnetic field strength of the baseline signals and the local magnetic field strength maximum of the first peak in the N400m time window.

We considered the first peak in the N400m time window in the extracted N400m signal for the latency measurement. However, for the amplitude measurement, we assessed N400m in the “unrelated” condition average of each subject, instead of the extracted N400m signal, in order to use the absolute value of N400m amplitude rather than the amplitude difference. The extracted N400m signal reflect the difference between “unrelated” and “related” conditions in which the N400m peak amplitude represents the amplitude difference between two conditions. This signal may be useful for more accurate measurements of the latency of N400m response, but may not be suitable for investigating inter-subject differences in processing amplitude.

**MRI Data Acquisition**

We acquired MRI scans at the Montreal Neurological Institute Brain Imaging Center in a Siemens Tim Trio 3T scanner using a 32-channel head coil. Head cushions were placed within the head coil to minimize subject’s head motion. Anatomical acquisition consisted of a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence 1mm isotropic three-dimensional acquisition with the following parameters: 192 sagittal slices,
256x256 matrix, TE=2.98 ms, TR=2.3 s, flip angle 9°. Diffusion MR images were obtained subsequently from 99 independent non-collinear directions (b-value of 1000 s/mm^2) and ten b = 0 images with no diffusion gradients which provides a reference for later image processing. In DTI, tensors are acquired at six or more different orientations of diffusion and are combined to calculate a single resulting DTI data. A high number of diffusion orientations such as 99 directions used in our acquisition ensures that high information content is available to calculate the diffusion tensor at each voxel.

**DTI Analysis**

We processed DTI data using Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library Diffusion Toolkit (FSL-FDT) (Smith et al., 2004, Jenkinson et al., 2012). We applied Eddy Current Correction tool for motion correction – DTI images were corrected to minimize distortions such as stretch, shears, and simple head motion using affine registration to a resting state volume (b_0 image) as a reference. We used Brain Extraction Tool to exclude non-brain tissues from the whole head images (Smith, 2002).

Diffusion tensors at each voxel were calculated using DTIFIT in order to generate FA maps. DTIFIT computed the diffusion tensor eigenvalues that described the diffusion coefficients in the primary, secondary and tertiary diffusion directions (eigenvectors).
In order to reconstruct the ILF in each subject, we used the ILF mask from a DTI-based white-matter atlas from Johns Hopkins University (Mori et al., 2005, Wakana et al., 2007, Hua et al., 2008)(http://lbam.med.jhmi.edu). This atlas is based on white matter tracts identified probabilistically by averaging 28 normal subjects’ deterministic tractography results. Each tractography involved multiple regions of interest defined based on existing anatomical knowledge. The reconstructed tracts were transformed into standard space and averaged to generate probabilistic maps of each major white matter tract. These probability maps show the probability of the presence of a tract at each voxel in Montreal Neurological Institute (MNI) space. The advantage of using the ILF mask from an atlas instead of manually defining regions of interest for each subject is that the number of voxels included in the ILF masks is equal throughout all subjects.

We transformed our subjects’ FA maps into the standard space and co-registered them with the ILF mask from the atlas (Figure 2). We visually inspected the co-registration quality, and subsequently applied the ILF mask as a volume of interest (VOI). In order to limit effects of voxels that fell in gray matter, we calculated a weighted average of the FA values of each voxel included in the VOI in the left and right hemispheres. Thus, instead of each included voxel contributing equally to the final mean FA, each voxel contributed according to the probability of including the ILF (\((\text{probability}_{\text{voxel}_1} \times \text{FA}_{\text{voxel}_1}), (\text{probability}_{\text{voxel}_2} \times \text{FA}_{\text{voxel}_2}), \ldots, (\text{probability}_{\text{voxel}_n} \times \text{FA}_{\text{voxel}_n}))\).
Statistical Analysis

We calculated the mean FA of reconstructed left and right tracts for each subject by averaging the FA values within all voxels included in the ILF mask using FSL utility (Fslutils) (Jenkinson et al., 2012). We used a one-tailed, paired t-test to examine if the mean FA in the left hemisphere is greater than in the right hemisphere, as previously described in the literature (Verhoeven et al., 2010, Thiebaut de Schotten et al., 2011, Menjot de Champfleur et al., 2012).
In order to examine inter-subject differences in ILF anisotropy and in efficiency of visual semantic processing, we applied a one-tailed Pearson’s correlation on the mean FA of the ILF in the hemisphere in which N400m is lateralized and N400m latency/amplitude for each subject. This allowed us to examine if efficient semantic processing correlates with higher anisotropy of the ILF.

Supplementary Analysis

We performed a supplementary analysis to assess the specificity of the ILF anisotropy effect on visual semantic processing. We evaluated auditory mismatch field (MMF) in order to clarify that the ILF does not have a general effect on cognitive functions. MMF is an ERF which reflects early cognitive auditory processing and does not involve semantic processing. It is activated at 150 - 250 ms after onset of the deviant stimulus in the primary and secondary auditory cortices and inferior frontal gyrus (Hari et al., 1984) which are not connected by the ILF. Since MMF is not localized in the ILF pathways, it is not expected to be associated with anisotropy of the ILF. Thus, we expect to see neither negative nor positive correlation between the ILF anisotropy and MMF response.

During the same MEG recording session, nonlexical sounds (bip/bop) were presented binaurally through earphones in an oddball paradigm in a 1:7 ratio; rare deviant stimuli (1) were interspersed amongst a series of frequent standard stimuli (7). These sounds did not contain lexical elements that would elicit any
language processing. Since MMF is evoked by the infrequent change in pitch, we extracted MMF response by subtracting the signals in the deviant condition average from the signals in the frequent condition (Jacobson, 1994, Alho, 1995).

We examined the correlation between the mean FA of the left ILF and MMF latency using a one-tailed Pearson’s correlation, and compared it to the correlation between the mean FA of the ILF and N400m latency in order to determine whether the effect of the ILF on visual semantic processing is due to a broad effect in cognitive processing.
Results

Behavioral Data

The reaction time corresponded to the time it took from the target word presentation to a subject’s response. The mean reaction time of all subjects was 627 ms (SD 113; range 437 ms - 838 ms) (Table 1). We calculated the accuracy of performance in the semantic decision task by counting the correctly responded trials over the total number of trials of four test blocks (240 trials). Late responses and wrong responses were considered incorrect. The mean accuracy of all subjects was 93.7 % (SD 5.3 %; range 80.0 % - 97.9 %) (Table 1). Mean FA of the left ILF did not show correlation with either reaction time [r(10) = -0.25, p > 0.05, R² = 0.06] or accuracy [r(10) = 0.13, p > 0.05, R² = 0.02] (Figure 3).

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Behavioural Data</th>
<th>Mean FA (ILF)</th>
<th>N400m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaction time (ms)</td>
<td>Accuracy (%)</td>
<td>Left</td>
</tr>
<tr>
<td>1</td>
<td>742</td>
<td>96.7</td>
<td>0.3850</td>
</tr>
<tr>
<td>2</td>
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<td>4</td>
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<td>80.0</td>
<td>0.4108</td>
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<tr>
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<td>0.4499</td>
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<tr>
<td>10</td>
<td>527</td>
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</tr>
</tbody>
</table>

Table 1: Summary of behavioural data, mean FA values and N400m.
Figure 3: Behavioural data and mean FA of the left ILF in 10 subjects. a) No correlation was found between reaction time and mean FA of the left ILF (p > 0.05). b) No correlation was found between accuracy and mean FA of the left ILF (p > 0.05).
MEG – N400m

N400m ERF was lateralized in the left hemisphere in all subjects. Four subjects showed similar fields in the right hemisphere, but of smaller magnitude as compared to the left hemisphere. The N400m latencies varied in time. The mean of N400m latency over all subjects was 441 ms (SD 46.7; range 350 ms – 500 ms) (Table 1). Figure 4 illustrates the extracted N400m signal of each subject, which contains an N400m peak with a signal-to-noise ratio higher than 1.5 in the N400m time window (300 - 500 ms). The amplitude of N400m was measured in the “unrelated” condition of all subjects, which is expected to evoke greater N400m. The mean of N400m amplitude over 10 subjects is 261 fT (SD 82.4; range 130 fT – 420 fT) (Table 1).
Figure 4: Individual N400m signals of all 10 subjects. These signals are subtractions of the “unrelated” condition average from the “related” condition average to reflect the N400m response only. The green signals represent activities determined from the left hemisphere and the blue signals represent activities determined from the right hemisphere. The red lines locate the time point used to measure N400m latency, which is the first peak in the N400m time window (300 ms – 500 ms).
FA Lateralization

The mean FA of the left and right ILF were compared to confirm the existence of a lateralization in agreement with the left lateralized visual semantic processing assessed by N400m. The mean FA of ILF was 0.415 (SD 0.021; range 0.385 – 0.450) in the left hemisphere and 0.403 (SD 0.028; range 0.350 – 0.444) in the right hemisphere. The lateralization index, ((left – right) / 0.5 (left + right)), was 0.029. Mean FA of the ILF was significantly greater in the left hemisphere than in the right hemisphere (one-tailed paired t-test, t(9) = 3.154, p < 0.05, Figure 5).
**Figure 5:** Lateralization of the inferior longitudinal fasciculus (ILF) determined by the mean fractional anisotropy (FA). Error bars represent standard deviation. The mean FA in left hemisphere is significantly higher than in the right hemisphere (p < 0.05).

**Correlations between Structure and Function**

We compared each subject’s mean FA of the ILF in the left hemisphere and N400m amplitude/latency in order to investigate the existence and degree of an ILF’s effect on visual semantic processing. There was no correlation between mean FA and N400m amplitude, r(10) = -0.30, p > 0.05, with a R^2 = 0.09 (Figure 6). However, there was a negative correlation between the mean FA of the left ILF and N400m latency, r(10) = -0.64, p < 0.05, with a R^2 = 0.41. In order to investigate whether the anisotropy of the ILF in visual semantic processing could affect other cognitive processing in the brain, we evaluated the latency of MMF. We found no correlation between the mean FA of the left ILF and the latency of MMF, r(10) = -0.09, p < 0.05, with a R^2 = 0.00 (Figure 7). This suggests that the
association of higher mean FA of the left ILF with a shorter latency of N400m response was less likely a global phenomenon or effect.

**Figure 6**: N400m amplitude and mean FA of the left ILF. No correlation between N400m amplitude and mean FA of the left ILF has been identified (p > 0.05).
Figure 7: N400m and MMF latencies and mean FA of the left ILF. A negative correlation between N400m peak latency and mean FA of the left ILF has been identified (p < 0.05).
Discussion

In the current study, we examined the role of the ILF in language comprehension using DTI and MEG. We hypothesized that the ILF plays a role in visual semantic processing and that efficient visual semantic processing is associated with high anisotropy of the ILF. Through a semantic categorization decision task in which subjects assessed the meaning of words, we measured N400m latency and amplitude as indices for visual semantic processing efficiency using MEG. We used FA as the index for the anisotropy of the ILF in DTI and reaction time and accuracy of the responses as behavioural indices for performance efficacy.

Our data showed a function and structure relationship of visual semantic processing (left-lateralized N400m and the leftward asymmetry of the ILF anisotropy) which agreed with previous studies (Helenius et al., 1998, Halgren et al., 2002, Billingsley-Marshall et al., 2007, Service et al., 2007, Lau et al., 2008, Verhoeven et al., 2010, Thiebaut de Schotten et al., 2011, Menjot de Champfleur et al., 2012). N400m latency negatively correlated with the mean FA of the ILF, which suggests that the ILF is associated with visual semantic processing. Our results confirm the recent findings on the ILF’s involvement in language, which included semantic processing (Mandonnet et al., 2007, Saur et al., 2008, Wong et al., 2011).

Wong and colleagues demonstrated a more specific role of the ventral language stream in language comprehension (Wong et al., 2011). In Wong’s study,
anisotropy of the ventral language pathway, including the ILF, positively correlated with performance in sound-to-word learning. The task involved hearing and learning foreign phonetic contrast for signalling word meaning, which tests acoustic processing and semantic processing. Our study supports that the ILF associated with semantic processing and extends this role to visual modality.

Although we do not know much about how the ILF affects the behavioural component of a function, we expected a negative correlation between reaction time and mean FA of the ILF, because efficient cognitive processing allows faster reaction time. Our findings did not confirm our expectation, although there was a trend toward the expected negative correlation. We also compared the accuracy of a participant’s response in the semantic decision task, but we could not confirm such a correlation. Although the obtained accuracy did not inform us about how the ILF affects semantic processing at the behavioural level, the high accuracy (all above 80% with 93.7% mean group accuracy) in performance confirmed participants’ comprehension and attention during the task.

The amplitude of N400m negatively reflects facilitated access of lexical information, which means that smaller amplitude underlies an increase in the efficiency of information transfer (Lau et al., 2009). Although, we expected the amplitude to be negatively correlated with the mean FA of the left ILF, we could not confirm that. However, the amplitude of N400m may not be the best index to assess the efficiency as it may not necessarily depend on the speed of the information transfer carried out by the white matter fibers. N400m amplitude may be mainly sensitive to the cognitive processing at the cortical level than to the
information transfer through subcortical connectivity.

The negative correlation between N400m latency and ILF anisotropy corroborates the current view on N400m latency (Helenius et al., 1998, Kitade et al., 1999). N400m latency, the speed at which the meaning of a word is processed in the brain, indicates the cognitive processing efficiency. The shorter the latency of N400m, the more efficiently information is transferred from the occipital lobe to the temporal lobe in which semantic processing takes place. Our data suggests that inter-individual differences in white matter tract connectivity and integrity are closely related to individual ability and efficiency of cognitive functions (Passingham et al., 2002, Johansen-Berg, 2010). Although various factors, such as semantic category of a word, level of engagement in processing, and frequency of a word, contribute to N400m amplitude changes, and the degree of how each factor influences the amplitude may vary at the individual level (Kiefer, 2001, Van Petten, 2006), N400m latency generally does not vary greatly. Only a few factors such as aging (i.e., longer latency in the aged individuals), neurological or psychiatric conditions, such as schizophrenia and Alzheimer’s disease (i.e., longer latency in neurological and psychiatric patients), and language proficiency (i.e., latency decreases with years of language experience and it increases with age of exposure) have been associated with N400m latency (Ardal et al., 1990, Grillon et al., 1991, Olichney et al., 2002, Moreno and Kutas, 2005, Federmeier, 2009).

We also evaluated the correlation between the ILF anisotropy and MMF latency. MMF reflects a process in which the infrequent sound is compared to the sensory memory trace that encodes the frequent sounds (Naatanen and Winkler,
Thus, this response indicates early cognitive auditory processing. MMF is a reasonable ERF for comparing to N400m, because they both reflect early cognitive processing at a pre-attentive level, which does not require active analysis or overt responses of the target stimuli (Holcomb, 1988, Naatanen et al., 1993, Deacon et al., 2000, Kiefer, 2002). Although MMF has been found to be sensitive to lexical elements of a presented stimulus (i.e., words elicit greater MMN amplitude than meaningless pseudo-words), it does not involve semantic processing of presented words as N400m does (Pulvermuller et al., 2001, Pulvermuller et al., 2004, Pulvermuller and Shtyrov, 2006). Moreover, in our protocol, subjects were binaurally exposed to sounds at different frequencies, which excludes any possible language processing. It is also important to note that MMF localizes in the primary and secondary auditory cortices and inferior frontal gyrus (Hari et al., 1984) which are not connected by the ILF. Our results showed that MMF latency did not correlate with the anisotropy of the ILF. This suggests that the role of the ILF is specific to visual semantic processing when compared to early auditory cognitive processing measured by MMF, and that this association is not a phenomenon due to a subject’s general cognitive processing ability or efficiency.

In our study, we have combined MEG mapping and DTI analysis; we recorded N400m using MEG for visual semantic processing efficiency and acquired the ILF anisotropy using DTI for structural connectivity. Linking these two techniques provided a powerful and effective tool, because it allowed us to
assess the relationship between functional and structural components of visual semantic processing in a non-invasive matter.

Despite a substantial increase in research of the organization of language at the cortical level using functional neuroimaging techniques (Vigneau et al., 2006), we still do not know much about the subcortical structure connecting the cortical language network. Subcortical connectivity is important in order to study how language function and structure are related, because the directly related white matter connections transmit information between brain areas in the functional network.

In summary, we have demonstrated that efficient visual semantic processing assessed by N400m latency is correlated with high ILF anisotropy. Our findings support the view that individual differences in white matter tract integrity reflects individual ability and efficiency of cognitive functions, because the white matter tracts connect and transmit information between brain areas in a functional network (Johansen-Berg, 2010). Combined, MEG and DTI techniques can identify key white matter tracts that contribute to functional networks and understand how they affect function.

**Limitations and Future Directions**

While this study shows a significant relationship between the efficiency of visual semantic processing and ILF anisotropy, there are some limitations that need to be acknowledged. First, our study included a small number of subjects.
Although obtained MEG and DTI data provided valid information even at the individual level (each subject elicited an evident signal of silent reading, including N100m/M170/N400m, and produced expected FA values from DTI data), statistical analysis greatly depend on the sample size. With a small sample size, there are more chances of obtaining results with type 1 (false positive) or type 2 (false negative) errors.

The second limitation in the study is the native language of subjects – not all our subjects were native English speakers, although they were all English proficient and studied in English post-secondary educational institution. N400m amplitude and latency have been found to be affected by language proficiency; higher amplitude and delayed latency are associated with lower language proficiency (i.e., nondominant language compared to dominant language) (Ardal et al., 1990, Matsumoto et al., 2005, Dobel et al., 2009). Non-native English speakers at the high proficiency level do not show a significant difference in brain responses as compared with native English speakers (Geyer et al., 2011, Leonard et al., 2011).

However, the words in the categorization semantic task consisted of commonly used and easily recognizable words. This task was easy for the subjects to complete, as mean accuracy in performance was 93.7% (SD: 0.05%). Whereas this ensured that subjects performed in the decision task without difficulty, this could have inserted a possible limitation to our study, because we were unable to observe significant inter-individual variations in accuracy.
Although we were able to observe that the mean FA of the ILF negatively correlated with N400m latency, it did not significantly correlate with reaction time, accuracy, and N400m amplitude. Thus, our task for measuring visual semantic processing may be suitable for group analysis to compare differences between “related” and “unrelated” conditions, but it may not be the best design for amplifying the inter-individual differences in processing efficiency. It may be more effective to use more complex visual lexical tasks, which require subjects to actively engage in cognitive processing or presented words.

Furthermore, in order to expand our knowledge of normal language functions and their structural basis, we still need to investigate the role of the ILF in the visual semantic processing in population with atypical language representation or language reorganization such as left-handed population and patients with neurological disorders, such as epilepsy and tumor (Duffau et al., 2008, Rodrigo et al., 2008, Wilke et al., 2010, Kim et al., 2011). In such patients with lesions in the ILF, we might be able to observe more prominent effects of the ILF in visual semantic processing and how the ILF’s function is compensated by other white matter connections. Extending the relationship between the ILF and visual semantic processing to the investigation of experience-dependent white matter plasticity may also be a compelling study. Some researchers have already demonstrated FA changes in adults following training and practices (Bengtsson et al., 2005, Scholz et al., 2009).

Our results demonstrate that the ILF’s role in semantic processing is not restricted to the previously described auditory modality, encompassing also visual
semantic processing. Our study further supports and extends current understanding on the ILF’s function in visual processing and language comprehension (Saur et al., 2008, Agosta et al., 2010, Wong et al., 2011, Ortibus et al., 2012, Taddei et al., 2012).
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