CHANGES IN BRAIN FUNCTIONAL CONNECTIVITY FOLLOWING DONEPEZIL TREATMENT IN ALZHEIMER'S DISEASE

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DEDICATION

To my Dad, whose passion for discovery is contagious, and to all the people along the way who made this work possible

# CHANGES IN BRAIN FUNCTIONAL CONNECTIVITY FOLLOWING DONEPEZIL TREATMENT IN ALZHEIMER'S DISEASE

by

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This study used resting state functional connectivity magnetic resonance imaging (fcMRI) to explore changes in brain connectivity and their behavior correlates in nine regions of interest (ROIs) in eleven patients with mild Alzheimer's disease (AD) following treatment with the cholinesterase inhibitor, donepezil. The ROIs were selected on the basis of their association with cholinergic neurotransmission, AD neuropathology, and neurocognitive deficits in AD. These ROIs included the medial septal nuclei, left and right hippocampi, left Broca's area and its right hemisphere homologue, left and right dorsolateral prefrontal cortices, and left and right primary visual cortices. Changes in connectivity were also related to changes in performance on neurocognitive tests of verbal fluency and episodic memory. Among the ROIs, the effects of the drug were selective. Only the connection between left and right DLPFC increased significantly after treatment. However, ten of the eighteen connections measured showed significant relationships between connectivity and behavior. The significant correlations centered around left hippocampus, left Broca's area, and dorsolateral prefrontal cortex bilaterally. Connections originating in the left hippocampus showed mostly inverse relationships with behavior. Predictions of selective increases in

connectivity in networks associated with the neurochemical, the neuropathological, and neurocognitive profiles of AD were generally not supported. A separate, whole-brain, exploratory, analysis measured changes in connectivity throughout the brain with each of the nine regions of interest (ROIs). There were increases in connectivity among bilateral frontal areas in language circuits, including the left IFG, left superior temporal gyrus, and left supramarginal gyrus, and in the sensory-motor integrative network. Further connections were noted between the left inferior frontal gyrus and caudate nucleus. The data suggest that the drug had selective effects on executive networks of attention.

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SPECT:
↑ ---increase
↓ ---decrease
A---anterior
ACG---anterior cingulate gyrus
BL---bilateral
DLFC---dorsolateral frontal cortex
DLPFC---dorsolateral prefrontal cortex
F-P---fronto-parietal
L--- left
P---posterior
P-T---parieto-temporal
R ---right
rCBF---regional cerebral blood flow
T-O---temporo-occipital
TPO---temporo-parieto-occipito

PET:
AGMABS---avg. glucose global metabolism in an axial brain slice
BA---Brodmann's Area
BGM---brain glucose metabolism
CGM---cerebral glucose metabolism
GM---glucose metabolism
nBM---nucleus Basalis of Meynert
RBGM---regional brain glucose metabolism
RGM---regional glucose metabolism
SI---substantia innominata

fMRI:
MFG---middle frontal gyrus
SFG---superior frontal gyrus
WM---working memory

# 1 INTRODUCTION

## 1.1 MAIN CONCEPTS

The aim of this study is to investigate changes in functional connectivity between key regions of the brain in Alzheimer's disease (AD) after treatment with the cholinesterase inhibitor donepezil. AD is the most common type of dementia (Cullum, Naugle, & Bigler, 1998) and is characterized by a gradual onset and a progressive, continuing decline of overall cognitive functioning.

Cognition is thought to involve distributed information processing, so that information is processed in multiple brain regions in parallel (Ramnani, Behrens, Penny, & Matthews, 2004). These regions work together as nodes within neural networks (Bressler, 1995), which provides the basis for the current project. According to this model, function is described in terms of the communication of neural information across areas within these networks. An index of the communication process between the nodes of these networks, functional connectivity, will be used as a measure of function. AD neuropathology affects multiple brain regions (Terry, Masliah, Salmon, Butters, DeTeresa, Hill, Hansen, & Katzman, 1991) and multiple cognitive systems. Thus, exploring functional connectivity within networks that underlie cognitive alterations of AD may add insight into functional characteristics of AD before and after drug treatment, indicating sites of drug action. The choice of networks selected for investigation is based on the neuroanatomy known to underlie specific cognitive functions affected in the disease as well as on the neurochemical deterioration and pathological progression that characterize the disease. The outcome measures are neurophysiological and behavior correlates of drug treatment in these patients.

Thus, the study integrates neurophysiological, neuroanatomical, and behavior information to elucidate the impact of donepezil treatment on functional characteristics of the disease.

Although AD pathology affects many regions of the brain, it typically begins in the mesial temporal lobe, specifically the hippocampus and entorhinal cortex (EC). It then spreads slowly outward to adjacent brain regions (Braak, Braak, Bohl, & Bratzke, 1998) to affect selected areas of the neocortex (Francis, Palmer, Snape, & Wilcock, 1999). Correspondingly, the earliest deficits are typically seen in memory and learning, with language, reasoning, and visuospatial deficits emerging later (Naugle, Cullum, & Bigler, 1998). The hallmark of the neuropathology of the disease is the development of senile plaques and neurofibrillary tangles, and loss of neuronal synapses and pyramidal neurons (Braak & Braak, 1991); these neural changes are considered to be the primary cause of the impairments in cognitive functioning and in behavior symptoms (Wenk, 2003).

Multiple neurotransmitter systems are implicated in the cognitive deficits seen in AD, but the most widely studied is the cholinergic system (Francis et al., 1999). Biochemical research beginning in the 1960s and 1970s identified cholinergic abnormalities in the brains of AD patients. These studies, combined with the apparent involvement of acetylcholine (Ach) in learning and memory, led to the cholinergic hypothesis of AD (Drachman & Leavitt, 1974), which postulates that deterioration in cholinergic basal forebrain neurons and a decrease in cholinergic neurotransmission in the cerebral cortex and other areas are responsible for the cognitive deficits and behavior changes characteristic of AD (Bartus, Dean, Beer, & Lippa, 1982).

Though our knowledge of the neuropathology of the disease has increased in recent decades, many questions about the nature of this neuropathology remain. While histopathological and molecular-biological studies have addressed various markers of neurotransmitters involved in AD neuropathology, investigations examining the integrity of the specific neurotransmitter pathways thought to be affected have been limited. Furthermore, limited research has been conducted on the nature of the connections within neuro-functional networks thought to be involved in AD. One way to identify these neuro-functional networks associated with the cognitive deficits of AD is to observe those connections whose connectivity improves after treatment with donepezil

Studies of AD neurochemical abnormalities have led to several pharmacological treatments that have shown some clinical efficacy (Sadock, Kaplan, & Sadock, 2003). The most widely used are acetylcholinesterase (AChE) inhibitors, one of which is donepezil (Imbimbo, Verdelli, Martelli, & Marchesini, 1999). Donepezil inhibits AChE, an enzyme that breaks down acetylcholine, but we do not have a clear understanding of its overall neurophysiological effects and the functional correlates of these effects. Donepezil prolongs the action of ACh at synapses, affecting the communication process between neurons within neuro-functional networks. Thus, a neurophysiological index that is sensitive to changes in this communication process should detect changes within networks thought to be affected by the drug. In the present study, functional connectivity magnetic resonance imaging (fcMRI), a tool for the non-invasive *in vivo* examination of neuro-functional networks, was used to investigate the effects of donepezil on brain function in 11 patients with mild AD.

In this study, there are five 'Networks' under investigation. They are made up of one ore more two-region pairs. These regions pairs are comprised of connections linking a seed region (e.g., left Broca's area) to a target region (e.g., right dorsolateral prefrontal cortex). Most of the experimental hypotheses involve all ipsilateral (e.g., left – left) and contralateral (e.g., left – right) connections between two regions, while some involve only a subset of the connections between two regions. Each of the region pairs that are subsets of the networks, their connections, and their abbreviations are listed in Table 1. The region pairs that are part of the experimental networks, and their associated connections will be referred to throughout the study by their abbreviations. The five experimental networks explored here share four characteristics: 1) the nodes in each network have known anatomical connections; 2) they are thought to be directly or indirectly implicated in cholinergic neurotransmission; 3) they are thought to be dysfunctional to some extent in AD; and 4) they are likely to be affected by donepezil treatment, based on evidence from multiple sources (neurochemistry, neurophysiology, neuroanatomy, and behavior). There are several rationales for the networks and their relationship to the cholinergic hypothesis of AD. The nodes of the first network to be explored communicate in part via the neurotransmitter acetylcholine. The network consists of the connections between the medial septal nuclei and the hippocampus. Plaques and tangles are very often found at both nodes of the second network, even in mildly impaired AD patients, and there is some evidence that pharmacological agents designed to treat the disease may have a direct effect on this neuropathology. The network consists of connections between the hippocampus and the dorsolateral prefrontal cortex (DLPFC). The third network is indirectly implicated in cholinergic transmission due to its involvement in

verbal fluency, a cognitive function that improves in AD patients after treatment with donepezil. This network connects Broca's area (BROCA), hippocampus (HIPP) and DLPFC. The fourth network subserves a behavior that is commonly improved by donepezil treatment, episodic memory. The network connects the medial septal nuclei (MEDSEP), HIPP, BROCA, and DLPFC. Finally, it is possible that donepezil may have a global effect on blood flow independent of an effect on neural metabolism, as well as a local effect on neural metabolism which would also result in a change in blood flow locally (Venneri, Shanks, Staff, Pestell, Forbes, Gemmell, & Murray, 2002). In order to control for a possible global effect of donepezil, functional connectivity in a network that is believed to be relatively uninvolved locally in the disease will be explored. The assumption is that the areas of this network should not be affected locally by the drug (or affected relatively less than any of the experimental networks), but should be influenced by a global drug effect. This network connects the left and right primary visual cortices. It has strong anatomical connections through the splenium of the corpus callosum, and tends to be unaffected until late stages of AD (Braak & Braak, 1996; Wong-Riley, Antuono, Ho, Egan, Hevner, Liebl et al., 1997), and has little to no response to donepezil.

## 1.2 REVIEW OF THE LITERATURE

### 1.2.1 Cholinergic hypothesis of AD

Multiple lines of evidence, from both human and animal studies, support a significant role of the cholinergic system in cognition. For instance, centrally active anticholinergic agents have been shown to produce cognitive deficits. Scopolamine, an anticholinergic agent acting on the central nervous system, was administered to a sample of young normal adult

subjects. Their performance on measures of learning and memory was significantly impaired, similar to the performance of a normal elderly sample on the same measures, and these effects were not due to sedation (Drachman & Leavitt, 1974). Similarly, subsequent placebo-controlled studies investigating the effects of scopolamine and another anticholinergic agent mecamylamine showed learning and memory and attentional impairments in young adults (Broks, Preston, Traub, Poppleton, Ward, & Stahl, 1988; Edginton & Rusted, 2003; Ellis, Ellis, Bartholomeusz, Harrison, Wesnes, & Erskine, 2005; Newhouse, Potter, Corwin, & Lenox, 1992; Rusted & Warburton, 1988; Wesnes, Simpson, & Kidd, 1988).

Work on laboratory animals has similarly shown a link between ACh and cognition. A number of studies have reported impaired performance on learning and memory tasks in rats after lesions to cholinergic basal forebrain regions (Berger-Sweeney, Heckers, Mesulam, Wiley, Lappi, & Sharma, 1994; Dekker, Connor, & Thal, 1991; Winkler, Suhr, Gage, Thal, & Fisher, 1995). Winkler et al. (1995) showed that ACh is a critical in normal cognition and for improving and restoring learning and memory following lesions to the nucleus basalis magnocellularis in rats, the analogue to the nucleus basalis of Meynert in humans. Compared to normal rats, those with lesions had longer escape latencies after 10 trials of performing the Morris water maze, a task known to reflect spatial learning and memory. Implantation of genetically modified cells that express acetylcholine in areas of the neocortex in lesioned rats resulted in reduced escape latencies. Other studies have also shown improvement in passive avoidance learning tasks in rats receiving transplanted cholinergic cells following lesions to the nucleus basalis magnocellularis (Dunnett, Toniolo, Fine, Ryan, Bjorklund, & Iversen,

1985; Gage & Bjorklund, 1986). Several animal investigations have examined levels of cholinergic markers after lesioning brain areas thought to be key sites of neuropathology in AD. For example, Kuhar, Sethy, Roth and Aghajanian (1973) showed that in the rat brain, lesions of the medial septal nuclei and of the diagonal band caused a 62% decrease in uptake of the Ach precursor, choline, in the hippocampus and a 22% reduction of uptake of choline in the neocortex.

Human postmortem brain studies also support the link between decreased cholinergic function and AD. Nilsson, Nordberg, Hardy, Wester, & Winblad (1986) found a decreased amount of ACh compared to controls. Loss of ACh-containing neurons in the brains of AD patients was shown by Whitehouse, Price, Struble, Clark, Coyle, & DeLong (1982), confirming earlier studies that indicated a significant reduction in choline acetyltransferase (ChAT) in postmortem AD brains (Bowen, Smith, White, & Davison, 1976; Davies & Maloney, 1976; Perry, Perry, Blessed, & Tomlinson, 1977). Perry et al. (Perry, Gibson, Blessed, Perry, & Tomlinson, 1977) found greater reduction of ChAT in the hippocampus relative to other areas examined when compared to patients with other types of dementia. Additional evidence for reduced cholinergic activity in AD was reported by Rylett, Ball, and Colhoun (1983), who found that cholinergic nerve cell endings from postmortem brain tissue had reduced choline uptake compared to normal controls. Similarly, numerous postmortem studies revealed a positive correlation between cholinergic markers (e.g., ChAT) and both level of impairment and density of neuropathological markers in AD patients (Francis, Palmer, Sims, Bowen, Davison, Esiri, Neary, Snowden, & Wilcock, 1985; Perry, Blessed, Tomlinson, Perry, Crow, Cross, Dockray, Dimaline, & Arregui, 1981).

### 1.2.2 Treatment of AD

The above findings led to the prediction that agents that stimulate central cholinergic function should improve cognitive deficits in AD patients (Francis et al., 1999; Mesulam, 2004; Summers, Majovski, Marsh, Tachiki, & Kling, 1986). There are a number of approaches to the treatment of the cholinergic deficit. Replacement of the ACh precursors choline and lecithin has been largely unsuccessful (Francis et al., 1999; Bartus, Dean, Sherman, Friedman, & Beer, 1981). AChE inhibition has produced the most encouraging results (Giacobini, 1997; Whitehouse, 1993). The first agent that demonstrated efficacy in improving learning and memory in AD patients was physostigmine (Weiner & Lipton, 2003). Studies using this agent have shown significant improvements in memory in AD patients (Mohs, Davis, Johns, Mathe, Greenwald, Horvath, & Davis, 1985; Summers et al., 1986; Thal, Masur, Blau, Fuld, & Klauber, 1989). Olton and Wenk (1987) reviewed studies on strategies to improve cognition in animals with lesions to the nucleus basalis magnocellularis and medial septal area. They also found the use of physostigmine demonstrated some success. Most studies, whether animal or human, have examined the efficacy of physostigmine on a short-term basis. Human studies exploring the long-term efficacy of physostigmine demonstrated limited improvement on formal neuropsychological measures of memory (Harrell, Callaway, Morere, & Falgout, 1990). Unfortunately, multiple research studies have found that physostigmine is associated with substantial gastrointestinal side effects (van Dyck, Newhouse, Falk, & Mattes, 2000).

Over the past two decades, clinical trials have been performed on several other AChE inhibitors, and four of these medications have since been approved by the Federal Drug

Administration for treatment of AD: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). The results of multiple efficacy studies of these agents suggest that groups of AD patients demonstrate significant global improvement compared to those treated with placebo (Doody, Dunn, Clark, Farlow, Foster, Liao, Gonzales, Lai, & Massman, 2001; Patterson, Gauthier, Bergman, Cohen, Feightner, Feldman, Grek, & Hogan, 2001; Patterson, Gauthier, Bergman, Cohen, Feightner, Feldman, & Hogan, 1999), though the definition of "meaningful clinical improvement" is heterogeneous across these studies (i.e. ranging from stabilization to marked improvement) (Lanctot, Herrmann, Yau, Khan, Liu, LouLou, & Einarson, 2003). AChE inhibitor treatment for cognitive and behavior deficits in AD has traditionally been considered to be a symptomatic intervention (Racchi, Mazzucchelli, Porrello, Lanni, & Govoni, 2004), but a treatment whose effects can be sustained up to one year (Racchi et al., 2004), and even 36 months (donepezil, rivastigmine, and galantamine) (Giacobini, 2000; 2001; 2002). Donepezil, the pharmacological agent used in this study, is reviewed next.

### 1.2.3 Donepezil

Donepezil produces several improvements in symptoms of AD patients. In a meta-analysis of individual patient data from randomized controlled trials, cognitive performance was significantly better in donepezil treated patients than in patients receiving placebo (Whitehead, Perdomo, Pratt, Birks, Wilcock, & Evans, 2004). Numerous studies have shown either significant cognitive improvements after treatment with donepezil or less decline compared to untreated patients or patients taking placebo (Burns, Rossor, Hecker, Gauthier, Petit, Moller, Rogers, & Friedhoff, 1999; Rogers, Doody, Mohs, & Friedhoff, 1998; Rogers,

Farlow, Doody, Mohs, & Friedhoff, 1998; Weiner, Martin-Cook, Foster, Saine, Fontaine, & Svetlik, 2000), and several studies have shown stabilization of daily activities and reduction in functional decline in AD patients treated with donepezil (Feldman, Gauthier, Hecker, Vellas, Subbiah, & Whalen, 2001; Mohs, Doody, Morris, Ieni, Rogers, Perdomo, & Pratt, 2001). Feldman and colleagues (2001) have also found that an AD sample had a significant improvement in behavior and neuropsychiatric symptoms after treatment with donepezil.

#### 1.2.3.1 Effects of donepezil/AChE inhibitors in AD neuropathology

In addition to their behavior effects, donepezil and other AChE inhibitors may have effects on rat cell cultures contaminated by samples of AD neuropathology in vitro (Racchi et al., 2004). Although there is little support for cholinergic depletion *causing* neurofibrillary tangles (NFTs) formation (and/or amyloidgenesis), "complex interactions of potentially profound pathophysiological significance" (Mesulam, 2004, p.47) are being identified between cholinergic neurotransmission and amyloid plaque/NFT formation (Frolich, 2002; Mesulam, 2004). In addition to the short-term symptomatic effect associated with reversing the cholinergic deficit, research using rat cell cultures suggests that AChE inhibitors also have an effect on AD neuropathology (Racchi et al., 2004). Specifically, these drugs may modulate the biochemical events that lead to the pathogenesis of the disease (Svensson & Giacobini, 2000). This influence of AChE inhibitors on neuropathology may be at least partly responsible for the improvement of cognitive and behavior functioning seen in some patients (Racchi et al., 2004).

Beta-amyloid (Aß) is one of the major neurotoxic components of the amyloid plaques in AD (Dickson, 1997; Lewis, Campbell, Terry, & Morrison, 1987). Donepezil and other

AChE inhibitors have been shown to slow down or limit the molecular events that lead to the production of Aß (Frolich, 2002; Svensson & Giacobini, 2000). Knots of tau protein comprise neurofibrillary tangles, a neuropathological marker in AD. In the normal brain, this protein assists in maintaining cell regulation by binding to the cell, while in AD, the tau proteins lose this capacity to maintain cell-regulation. Instead, they self-aggregate (Rosenberg, 2000). There may be a relationship between AChE and NFT formation via increased levels of ACh at synapses. Sadot et al. (1996) showed that when muscarinic receptors are stimulated, there are disruptions in biochemical events that lead to the decreased capacity of tau to assist in maintaining cell function. Another role of AChE inhibitors in NFT formation is through their effects on AChE. Light and electron microscope studies show AChE activity in NFTs (Svensson & Giacobini, 2000). AChE inhibitors can inhibit the action of AChE in NFTs (Mesulam, 2000; Mesulam, Carson, Price, & Geula, 1992), and this links AChE inhibitors directly to NFT formation.

Formation of NFTs, neuronal loss, decrease in dendritic extent, and synaptic depletion all alter and disturb the communication among various cortical areas. Although the mechanism of cortical disconnection remains to be validated (Mosconi, Pupi, De Cristofaro, Fayyaz, Sorbi, & Herholz, 2004), the alteration in connectivity results in anatomic isolation and fragmentation of many cortical zones (De Lacoste & White, 1993; Mielke, Schroder, Fink, Kessler, Herholz, & Heiss, 1996). This disconnection can be studied using functional connectivity measures. The progression of the disease is associated with decline in functional connectivity. The effect of the drug should reflect an increase in functional connectivity.

#### 1.2.3.2 Other targets of AChE inhibitors/donepezil

In addition to preventing the breakdown of ACh at the synapse and modulating cellular processes in AD, contributions to the clinical efficacy of AChE inhibitors have been identified. PET studies report that long-term tacrine treatment can increase the number of nicotinic receptors in AD brains (Nordberg, Lilja, Lundqvist, Hartvig, Amberla, Viitanen, Warpman, Johansson, Hellstrom-Lindahl, Bjurling, & et al., 1992). Evidence for another possible target of AChE inhibitors comes from biochemical studies showing that donepezil binds to an activator site on the nicotinic receptor, suggesting that this process may contribute to the clinical efficacy of these agents (Svensson & Giacobini, 2000). Furthermore, electrophysiological studies have reported that physostigmine and galantamine significantly increase the opening frequency of nicotinic receptors in hippocampal cell preparations (Maelicke, Coban, Storch, Schrattenholz, Pereira, & Albuquerque, 1993; Pereira, Alkondon, Reinhardt, Maelicke, Peng, Lindstrom, Whiting, & Albuquerque, 1994).

AChE activity is often used as a marker of the amount of ACh available at synapses, such that the less the AChE activity, the more the availability of ACh. However, the level of AChE activity is not sufficient to predict extracellular levels of ACh following treatment with AChE inhibitors (Messamore, Warpman, Ogane, & Giacobini, 1993). This suggests that increased cholinergic neurotransmission following AChE inhibitor treatment is attributable not only to the inhibition of AChE, but also to additional factors, such as this nicotinic agonistic effect (Nilsson, Adem, Hardy, Winblad, & Nordberg, 1987).

Muscarinic and nicotinic receptors exist on cholinergic nerve terminals and on monoaminergic nerve terminals. For example, tacrine enhances dopamine neurotransmission

in muscarinic and nicotinic nerve terminals in the rat brain (Warpman, Zhang, & Nordberg, 1996). Similarly, donepezil increases ACh, norepinephrine, dopamine and serotonin levels in the rat cortex (Svensson & Giacobini, 2000). It is possible, then, that the efficacy of these agents to improve cognitive functioning may be at least partly attributable to increasing other neurotransmitter levels (Svensson & Giacobini, 2000).

### 1.2.4 AChE Inhibitors and Functional Neuroimaging in AD

There are relatively few studies investigating the functional changes that occur in the brain after AChE inhibitor treatment. In this study, 'function' is defined as correlated fluctuations in signal between areas. However, in the majority of studies on the effects of AChE inhibitors on brain function (i.e. those reviewed in this section), 'function' is defined as activity recorded at rest, rather than during performance of a specific task. A minority of these studies define 'function' as increased activation during the performance of a task after AChE inhibitor treatment, compared to baseline. The relationship between increased activity in two areas due to pharmacological treatment, on the one hand, and correlated signal between these two areas due to the treatment, on the other, is unclear. However, a review of these studies is important as they speak to the impact of AchE inhibitors on human brain function in vivo.

Functional imaging studies vary across a host of imaging modalities and experimental variables, including specific drug used, dosing levels, degree of cognitive impairment, length of treatment, time-interval between scans, control conditions, and subject selection (e.g., responders versus non-responders). The AD subjects in these studies were often restricted to mildly impaired patients. Some of these studies explored differences between responders

and non-responders to treatment. The control groups ranged from untreated or placebo-treated patients to normal elderly subjects without treatment. The present review includes results of both short-term (e.g., after single dose) and long-term treatment studies using single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). The presence of effects for these studies will be noted in the text, while details on the particular drug used, direction of the drug effects, interval between pre- and post-treatment scans, composition of subject sample(s), and number of subjects in sample(s), is specified in Table 2.

#### 1.2.4.1 SPECT studies

Cholinesterase inhibition increases cerebral blood flow (rCBF) in AD patients through a direct effect on cerebral blood vessels, and stimulates neuronal activity regionally (Venneri et al., 2002). Longitudinal SPECT studies exploring the effects of AChE inhibitors after 6 months to 1 year predominantly show increases in blood flow or no change in blood flow. A finding of no change in blood flow relative to a decline in untreated AD controls was interpreted as the drug preventing progression of the disease (Nakano, Asada, Matsuda, Uno, & Takasaki, 2001; Nobili, Vitali, Canfora, Girtler, De Leo, Mariani, Pupi, & Rodriguez, 2002).

Most SPECT studies of AChE inhibitors on blood flow in AD show global effects (Gustafson, Edvinsson, Dahlgren, Hagberg, Risberg, Rosen, & Ferno, 1987; Harkins, Taylor, & Mattay, 1996; Staff, Gemmell, Shanks, Murray, & Venneri, 2000), diffuse (Tune, Brandt, Frost, Harris, Mayberg, Steele, Burns, Sapp, Folstein, Wagner, & et al., 1991; Venneri et al., 2002) or multifocal (Hunter, Wyper, Patterson, Hansen, & Goodwin, 1991; Lojkowska,

Ryglewicz, Jedrzejczak, Minc, Jakubowska, Jarosz, & Bochynska, 2003; Nakano et al., 2001) in frontal (Tune et al., 1991; Venneri et al., 2002), temporal (Nobili et al., 2002; Venneri et al., 2002), and parietal regions (Lojkowska et al., 2003; Tune et al., 1991; Venneri et al., 2002). Here, 'diffuse effects' refer to large foci of increased rCBF spanning several lobes, while 'multifocal effects' refers to rCBF increases in multiple regions of interest (ROIs).

Of the few studies finding specific localized effects, the most consistent is in frontal areas bilaterally (Ceravolo, Volterrani, Tognoni, Dell'Agnello, Manca, Kiferle, Rossi, Logi, Strauss, Mariani, & Murri, 2004; Ebmeier, Hunter, Curran, Dougal, Murray, Wyper, Patterson, Hanson, Siegfried, & Goodwin, 1992; Hunter et al., 1991; Staff et al., 2000; Venneri et al., 2002). Some of those studies did not use a control group (Ceravolo et al., 2004; Staff et al., 2000). The three that did use control groups found increased (relative) activation in the superior frontal region, (Ebmeier et al., 1992), in the medial frontal region (Venneri et al., 2002), and in the frontoparietal region (Hunter et al., 1991). A less consistent finding is an increase in parieto-temporal or temporo-parieto-occipital regions (Geaney, Soper, Shepstone, & Cowen, 1990; Gustafson et al., 1987). Issues relating to choice of control group limit the relevance of these studies to this experiment. For a more detailed review of these SPECT findings, please see Table 2.

Some of the studies above explored the relationship between perfusion changes after AChE treatment and cognitive test performance. For instance, Hunter et al.(1991) found a correlation between an increase in rCBF in a left frontal-temporal area and change in performance on the MMSE after AChE inhibitor treatment in AD (Nobili et al., 2002).

Others have shown an effect on both blood flow and MMSE performance (Harkins et al., 1996; Nakano et al., 2001; Venneri et al., 2002). Of particular relevance to this project, some studies showed an effect on blood flow and letter fluency (Lojkowska et al., 2003). Other measures of cognitive functioning improve as well in concert with increases in blood flow following AChE inhibitor treatment, including digit span (Nakano et al., 2001; Venneri et al., 2002), Raven's Progressive Matrices (Venneri et al., 2002) and the Trail Making Test A (Lojkowska et al., 2003). However, these latter studies did not report a correlation between blood flow and performance on these measures.

In sum, despite numerous design differences across these studies, the most consistent findings among them are a global effect, or a specific effect in frontal lobe areas. Some also show effects on measures of cognitive functioning in addition to an effect on cerebral blood flow, as well as a correlation between the two.

#### 1.2.4.2 PET studies

PET studies have explored the effects of a variety of AChE inhibitors (e.g., donepezil, physostigmine, rivastigmine, tacrine) on glucose metabolism and/or AChE activity in mild-moderate AD. As in SPECT studies, lack of change in glucose metabolism in treated patients relative to a decline in placebo-treated patients was interpreted as a positive effect of the drug (Tune, Tiseo, Ieni, Perdomo, Pratt, Votaw, Jewart, & Hoffman, 2003). Most studies found multiple localized effects in frontal, temporal, and parietal regions (Kaasinen, Nagren, Jarvenpaa, Roivainen, Yu, Oikonen, Kurki, & Rinne, 2002; Nordberg, Amberla, Shigeta, Lundqvist, Viitanen, Hellstrom-Lindahl, Johansson, Andersson, Hartvig, Lilja, Langstrom, & Winblad, 1998; Tune et al., 2003), as well as in the hippocampus and

putamen (Nordberg et al., 1998). One study uncovered a generalized positive cortical effect in AD patients relative to a normal control group (Shinotoh, Aotsuka, Fukushi, Nagatsuka, Tanaka, Ota, Tanada, & Irie, 2001). This study explored AChE inhibition, and found that AChE activity was reduced by 39% during treatment in AD patients relative to no change in untreated normal controls. Instead of using AChE activity, several studies found a global decrease in glucose metabolism relative to normal controls (Blin, Ivanoiu, De Volder, Michel, Bol, Verellen, Seron, Duprez, & Laterre, 1998; Blin, Piercey, Giuffra, Mouradian, & Chase, 1994).

With respect to cognitive performance, some studies showing effects on AChE activity or glucose metabolism also show improvement on global cognitive measures (e.g., ADAS-Cog; Shinotoh et al., 2001) and on measures of attention (e.g., digit span; Nordberg et al., 1992). Of particular relevance to the present study, which focuses on the relationship between change in cortical activity and change in behavior, findings from several studies revealed a correlation between change in cortical inhibition of AChE and change in performance on the Stroop Color Word Interference Test, a measure of executive functioning, after donepezil treatment (Bohnen, Kaufer, Hendrickson, Ivanco, Lopresti, Koeppe et al., 2005). In sum, the studies above suggest both multiple localized effects in frontal, temporal and parietal regions as well as a global effect of AChE inhibitors in AD. (For a review of the main findings from PET, please see Table 2).

#### 1.2.4.3 fMRI studies

Two fMRI studies have investigated the effects of AChE inhibitors on functional change. Saykin et al. (2004) explored the effects of donepezil during a working memory task

in a sample of patients with mild cognitive impairment (MCI). They found that after donepezil treatment, increased activation relative to baseline was seen primarily in the dorsolateral prefrontal cortex. In addition, relative to controls, MCI patients showed increased activity in the left superior frontal gyrus. Furthermore, this increase in frontal activity correlated with improved performance on the working memory task. Another experiment by Rombouts et al. (2002) investigated the effects of rivastigmine during face-encoding and working memory tasks. They found increased activation in the fusiform gyrus. Increases were seen in the left middle and left superior frontal gyri during 'simple working memory', and in the left middle frontal gyrus, right superior frontal gyrus, and right inferior frontal gyrus for the 'increased-working memory' condition. Thus, these studies show consistent frontal effects of AChE inhibitors during working memory tasks. This suggests that the frontal effects of AChE inhibitors in AD will be reflected in functional changes in activity in the regions explored in this study, namely the inferior frontal gyrus (IFG) and the DLPFC (See Methods section below).

#### 1.2.4.4 Summary of imaging studies

SPECT, PET and fMRI studies show both global effects and local effects. The most consistent specific localized finding is increased frontal brain activity (Ceravolo et al., 2004; Ebmeier et al., 1992; Hunter et al., 1991; Rombouts et al., 2002; Saykin et al., 2004; Staff et al., 2000; Venneri et al., 2002). A less consistent specific localized finding is an effect in temporal regions (Geaney et al., 1990; Gustafson et al., 1987). The research reviewed above most clearly suggests that the effects of AChE inhibitors in the AD sample of the present study will be reflected in functional changes in frontal ROIs, namely the IFG, DLPFC, and

anterior cingulate gyrus. It is also expected that AChE inhibitors will effect changes in temporal regions, namely hippocampus and entorhinal cortex in AD (See Methods section below). Lastly, the relatively limited effect of AChE inhibitors in the primary visual cortex can be expected to be reflected in unchanged functional connectivity within the primary visual cortex (See Methods section below).

An important caveat is that even studies using the same imaging technique, the same patient population and same class of drug may reach divergent conclusions about areas activated due to differences in other experimental variables. These include level of impairment, specific drug used, length of treatment, and ROIs. Therefore, the comparability and generalizability of such studies are limited, and interpretations should be made with caution. Similarly, although a few studies show reduced metabolism (Blin et al., 1998), most studies show increased metabolism following administration of AChE inhibitors. In the present study, findings from the latter investigations offer support for choices of ROIs for the present analysis of functional connectivity.

### 1.2.5 Functional Connectivity

Early studies using implanted electrodes and other techniques in live animals demonstrated the existence of periodic oscillations in cerebral blood flow (Dora & Kovach, 1981; Vern, Schuette, Leheta, Juel, & Radulovacki, 1988). Similar fluctuations in regional cerebral blood flow have been detected in humans and appear to be of the same origin as those in animals (Haughton & Biswal, 1998). Such fluctuations in blood flow have been linked to EEG activity in both humans and animals (Cooper, Crow, Walter, & Winter, 1966; Golanov, Yamamoto, & Reis, 1994). Oscillations in baseline signal intensity have also been

observed in BOLD fMRI brain activation studies (Jezzard, Heineman, Taylor, DesPres, Wen, Balaban, & Turner, 1994). Numerous reports suggest that low frequency synchronous fluctuations are a general phenomenon representing the functional connection of cortical areas (e.g., Bressler, 1995). Specifically, these signal fluctuations may reflect alterations in blood flow and oxygenation that are coupled with neural activity (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002; Haughton & Biswal, 1998).

The idea that synchronized signal fluctuations in multiple regions of the brain reflects functional connectivity is consistent with the parallel model of human information processing (Bressler, 1995). Brain regions are known to process information in parallel, to exchange information via feedforward and feedback loops and to convey information by synchronized oscillatory coupling of neural assemblies (Singer, 1995). Exploring the synchrony between oscillatory fluctuations in BOLD fMRI signal depends on the assumption that these synchronous fluctuations are a reflection of the coherence, or functional connectivity, between the underlying oscillating neural assemblies (Singer, 1995). Consequently, the degree to which fluctuations in one region are similar to fluctuations in another region may provide insight into neural connectivity (Hampson et al., 2002).

A number of studies have explored the patterns of resting-state temporal fluctuations in MR signal. In particular, correlations have been found between the signal fluctuations in a reference region and the signal fluctuations in other parts of the brain using fMRI. Functional connectivity magnetic resonance imaging (fcMRI) is a term for this technique. In the earliest fcMRI investigation, Biswal, Yetkin, Haughton, & Hyde (1995) reported that resting-state low-frequency BOLD signal fluctuations are highly synchronized in

neighboring voxels in functionally related regions of the brain but not in unrelated brain regions. Consistent with that view, they found correlated resting-state signal fluctuations between the left and right sensorimotor cortex and supplementary motor area. They also found extensive spatial overlap between these areas with correlated low-frequency fluctuations in signal and regions activated during bilateral finger tapping, linking anatomical connectivity with functional connectivity (Biswal et al., 1995). Other researchers have used fcMRI and confirmed correlations between homologous motor regions (Cordes, Haughton, Arfanakis, Wendt, Turski, Moritz, Quigley, & Meyerand, 2000; Xiong, Parsons, Gao, & Fox, 1999), as well as between primary auditory cortices (Biswal et al., 1995) and between primary visual cortices (Cordes et al., 2000; Lowe, Mock, & Sorenson, 1998). Extending these studies to non-homologous regions, fcMRI has also been used to explore functional connectivity within other networks with known anatomical connections (Waites, Stanislavsky, Abbott, & Jackson, 2004), including subcortical regions (Allen, McColl, Barnard, Ringe, Fleckenstein, & Cullum, 2005; Stein, Moritz, Quigley, Cordes, Haughton, & Meyerand, 2000) and the language system (Cordes et al., 2000; Hampson et al., 2002). Such fcMRI techniques have by now been applied to study schizophrenia (Lawrie, Buechel, Whalley, Frith, Friston, & Johnstone, 2002), the effects of cocaine administration (Li, Biswal, Li, Risinger, Rainey, Cho, Salmeron, & Stein, 2000), multiple sclerosis (Lowe, Phillips, Lurito, Mattson, Dzemidzic, & Mathews, 2002), and acquired cerebral lesions (Quigley, Cordes, Wendt, Turski, Moritz, Haughton, & Meyerand, 2001). To date, there have been two studies exploring resting-state functional connectivity in AD using fcMRI (Allen, Barnard, McColl, Lipton, McDonald, Rubin, et al., 2003; Li, Li, Wu, Zhang,

Franczak, & Antuono, 2002). These studies will be discussed in the following section describing connectivity abnormalities in AD. However, the main focus of this study is on change in connectivity due to pharmacological treatment.

### 1.2.6 AD neuropathology

The presence of abundant NFTs, neuritic plaques (NPs) and neuronal synaptic loss are viewed as the main neuropathological hallmarks of AD (Giannakopoulos, Herrmann, Bussiere, Bouras, Kovari, Perl, Morrison, Gold, & Hof, 2003). NFTs and NPs have consistently been found in the AD brain, specifically in the entorhinal cortex (EC), hippocampal formation, and Brodmann's area (BA) 9 (Cras, Smith, Richey, Siedlak, Mulvihill, & Perry, 1995; Giannakopoulos et al., 2003; Gomez-Isla, Hollister, West, Mui, Growdon, Petersen, Parisi, & Hyman, 1997). Although NFTs and NPs are present in the post-mortem brains of older individuals who do not meet clinical criteria for AD during life (Berg, McKeel, Miller, Storandt, Rubin, Morris, Baty, Coats, Norton, Goate, Price, Gearing, Mirra, & Saunders, 1998; Braak & Braak, 1991; Dickson, Crystal, Mattiace, Masur, Blau, Davies, Yen, & Aronson, 1992), NPs are significantly more common in AD brains (Davis, Schmitt, Wekstein, & Markesbery, 1999; Knopman, Parisi, Salviati, Floriach-Robert, Boeve, Ivnik, Smith, Dickson, Johnson, Petersen, McDonald, Braak, & Petersen, 2003; Morris, Storandt, McKeel, Rubin, Price, Grant, & Berg, 1996). In addition, neuropathology is distributed more densely in the neocortex of AD brains (Lewis et al., 1987). Furthermore, postmortem studies have found the presence of NPs in the brains of AD patients who had at least mild impairment (Tiraboschi, Sabbagh, Hansen, Salmon, Merdes, Gamst, Masliah, Alford, Thal, & Corey-Bloom, 2004), suggesting that the presence of neuropathological

markers characterizes patients with early AD. Other markers include declining central nervous system cholinergic functioning and extensive reductions in specific neuronal populations and synapses. These alterations have been associated with level of impairment/cognitive deficits in AD (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Blessed, Tomlinson, & Roth, 1968; Cummings & Kaufer, 1996). The hippocampus, entorhinal cortex, and BA 9 consistently show systematic and selective degeneration, which is associated with AD cognitive deficits. Connectivity dysfunction between elements of this network will be discussed in the following section.

### 1.2.7 Measures of connectivity in AD

AD compromises the integrity of long cortico-cortical association fibers at points of origin and termination (Esiri, Pearson, & Powell, 1986; Lewis et al., 1987). Disruptions of synaptic connections are also considered to underlie the disease (Masliah & Terry, 1993). Coherence abnormalities in AD have been determined with EEG (e.g., Jeong, 2004; Leuchter, Newton, Cook, Walter, Rosenberg-Thompson, & Lachenbruch, 1992), while functional connectivity abnormalities have been shown with fcMRI (e.g., Allen et al., 2003 ; Li et al., 2002), and PET (e.g., Becker, Mintun, Aleva, Wiseman, Nichols, & Dekosky, 1996; Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001; Mosconi et al., 2004). Similarly, reduction of white matter fiber tract integrity has been shown with diffusion tensor imaging (DTI) (e.g., Bozzali, Falini, Franceschi, Cercignani, Zuffi, Scotti, Comi, & Filippi, 2002; Rose, Chen, Chalk, Zelaya, Strugnell, Benson, Semple, & Doddrell, 2000). Also, animal lesion studies have led to hypotheses about connectivity dysfunction in AD (e.g., Cotman,

Matthews, Taylor, & Lynch, 1973; Ikonomovic, Mufson, Wuu, Cochran, Bennett, & DeKosky, 2003).

Coherence analysis of EEG has been used to estimate the degree of functional connectivity among cortical areas. Coherence is a linear measure of the correlations between two signals as a function of frequency (Nunez, Silberstein, Shi, Carpenter, Srinivasan, Tucker, Doran, Cadusch, & Wijesinghe, 1999; Stam, van der Made, Pijnenburg, & Scheltens, 2003). Decreased coherence reflects reduced functional connections between cortical areas beneath the electrodes or reduced common modulation of two areas (Jeong, 2004). Most studies report a decrease of coherence in the alpha band in AD (Berendse, Verbunt, Scheltens, van Dijk, & Jonkman, 2000; Besthorn, Forstl, Geiger-Kabisch, Sattel, Gasser, & Schreiter-Gasser, 1994; Locatelli, Cursi, Liberati, Franceschi, & Comi, 1998), suggesting reduced functional connections between cortical regions (Jeong, 2004). Furthermore, these abnormalities are correlated with severity of impairment (Hughes, Shanmugham, Wetzel, Bellur, & Hughes, 1989; Kowalski, Gawel, Pfeffer, & Barcikowska, 2001). By exploring statistical dependencies between two time series, Jeong, Gore, & Peterson (2001) found a decrease in functional connectivity in AD patients, particularly over the frontal and anterior-temporal regions. Several authors have suggested that loss of long-distance association fibers might explain the changes in EEG coherence in AD (Cook & Leuchter, 1996; Jeong, 2004; Stam et al., 2003).

Some studies support a relationship between the cholinergic deficit and EEG coherence. For example, blocking of the cholinergic system by scopolamine reduces resting EEG coherence in humans (Kikuchi, Wada, Koshino, Nanbu, & Hashimoto, 2000).

Furthermore, an increase in the slow band power in AD is associated with a cortical loss of ChAT (Reinikainen, Riekkinen, Paljarvi, Soininen, Helkala, Jolkkonen, & Laakso, 1988; Soininen, Reinikainen, Partanen, Helkala, Paljarvi, & Riekkinen, 1992). Also, anti-cholinergic drugs in healthy subjects induce an increase in coherence of slow bands (Kikuchi et al., 2000). Stam et al. (2003) suggest that if the loss of synchronization in AD would simply be caused by a loss of neurons, it would be difficult to understand why all frequencies are not equally affected. Thus, the pattern of frequency-specific decreases in EEG synchronization suggests an important role of cortical cholinergic denervation. However, at the same time, the spatial resolution of standard scalp-recording EEG signal is poor, and techniques with better spatial resolution, like fcMRI or PET, are necessary to explore relationships between specific cortical structures (Lowe et al., 1998).

fcMRI studies of AD have demonstrated a reduction in correlated low-frequency fluctuations relative to other populations in selective regions. Li et al. (2002) explored low-frequency fluctuations in the hippocampus in early AD relative to patients with mild cognitive impairment (MCI) and normal controls, and found a reduction in functional connectivity in that region in AD patients relative to the two other groups. In this investigation, the primary visual cortex was used as a control region. Allen et al. (2003) also explored functional connectivity in mildly impaired AD patients and found decreased functional connectivity between hippocampi and between hippocampus and a variety of cortical and subcortical regions. In the present study, this work is extended by testing hypotheses regarding connectivity within specific networks after donepezil treatment.

PET studies exploring functional connectivity in AD have examined correlated signal fluctuations in functionally related structures during resting state and during performance of cognitive tasks (Becker et al., 1996; Desgranges, Baron, Giffard, Chetelat, Lalevee, Viader, de la Sayette, & Eustache, 2002; Grady et al., 2001; Grady, McIntosh, & Craik, 2003; Herbster, Nichols, Wiseman, Mintun, DeKosky, & Becker, 1996; Horwitz, McIntosh, Haxby, Furey, Salerno, Schapiro, Rapoport, & Grady, 1995; Mosconi et al., 2004). Of these, several studies have focused on small brain structures/regions such as the EC (Mosconi et al., 2004), prefrontal cortex and amygdala (Grady et al., 2001). For example, Mosconi and colleagues (2004) explored at-rest functional connectivity between the EC and the rest of the brain in AD on the basis of known anatomical pathways identified in animal studies. They found that in normal controls, consistent with known anatomic connections, there were significant bilateral correlations between signal in the EC and signal in other limbic cortical regions (Mosconi et al., 2004). However, in AD they found that the only preserved EC-cortical functional connections were with the inferior temporal and occipital areas and only on the ipsilateral side. Thus, relative to normal controls, they found a significant loss of functional connectivity between the EC and several cortical and limbic regions (Mosconi et al., 2004). Another PET experiment by Grady et al. (2001) explored functional connectivity in AD. First, areas of activation during a face encoding task in normal volunteers and mildly impaired AD patients were identified. Next, areas of activation that showed the highest correlations with task performance were identified, implicating the right prefrontal cortex and the left amygdala. Last, they explored resting-state functional connectivity between the right prefrontal cortex and the rest of the brain, and between the

amygdala and the rest of the brain in both groups. In controls, activity in the right prefrontal cortex was positively correlated with blood flow in the left prefrontal cortex, bilateral extrastriate and parietal areas, as well as the right hippocampus. However, in patients, activity in the right prefrontal cortex was correlated mainly with other prefrontal regions. They interpreted the results as support for functional disconnection between the prefrontal cortex and the hippocampus in AD and suggested that memory breakdown in early disease stages is related to a reduction in the integrated activity within a distributed network that includes these two areas.

New MR techniques such as diffusion tensor imaging (DTI) and magnetization transfer imaging have revealed important insights into the structural white matter tissue changes that occur in AD (van der Flier, van den Heuvel, Weverling-Rijnsburger, Bollen, Westendorp, van Buchem, & Middelkoop, 2002). By calculating the degree of diffusion of water molecules along white matter fiber tracts, DTI studies can explore the integrity of these tracts (Kantarci, Jack, Xu, Campeau, O'Brien, Smith, Ivnik, Boeve, Kokmen, Tangalos, & Petersen, 2001). Previous pathological studies of AD have shown that white matter abnormalities, such as the loss of axons and oligodendrocytes (which surround and provide support for axons), are often seen in white matter (Brun & Englund, 1986). DTI studies have shown severe white matter structural changes in AD (Bozzali et al., 2002; Bozzali, Franceschi, Falini, Pontesilli, Cercignani, Magnani, Scotti, Comi, & Filippi, 2001; Hanyu, Sakurai, Iwamoto, Takasaki, Shindo, & Abe, 1998; Rose et al., 2000; Takahashi, Yonezawa, Takahashi, Kudo, Inoue, & Tohgi, 2002; Yoshiura, Mihara, Ogomori, Tanaka, Kaneko, & Masuda, 2002). For example, Rose and colleagues (2000) found that relative to normal

controls, patients with probable AD showed a significant reduction in the integrity of the association white matter fiber tracts, such as the splenium of the corpus callosum and superior longitudinal fasciculus. Similarly, others have found a reduction in white matter integrity in the frontal, temporal and parietal lobes in AD patients (Bozzali et al., 2001). Another DTI report revealed reduced white matter integrity around the anterior and posterior cingulate gyrus in AD (Takahashi et al., 2002).

As mentioned above, NFTs are thought to develop first in the entorhinal-transentorhinal area, followed by a progressive spread through the hippocampus and into the neocortex (Braak & Braak, 1991; Delacourte, David, Sergeant, Buee, Wattez, Vermersch, Ghozali, Fallet-Bianco, Pasquier, Lebert, Petit, & Di Menza, 1999). The disconnection between the EC and the hippocampus (i.e., perforant pathway), which specifically reflects glutamatergic input, is hypothesized to be a primary event that occurs in AD (Ikonomovic et al., 2003). Support for this disconnection hypothesis comes from lesion studies in rats which have shown that lesions to the EC induce sprouting of cholinergic fibers from the medial septal nuclei into hippocampal regions to replace lost entorhinal glutamatergic innervation of the hippocampus (Cotman et al., 1973; Ikonomovic et al., 2003). Ikonomovic and colleagues (2003) suggest that the septal cholinergic projections are capable of synaptic reorganization and increased synthesis of ChAT in response to entorhinal-hippocampal disconnection. They further postulate that as the disease process continues, this compensatory response subsequently fails, leading to the decline in hippocampal ChAT levels as seen in people with mild AD (DeKosky, Ikonomovic, Styren, Beckett, Wisniewski, Bennett, Cochran, Kordower, & Mufson, 2002). Continued impairment of this putative compensatory mechanism then

results in further decreases of hippocampal ChAT activity, as demonstrated in a cohort of end-stage AD cases (Ikonomovic et al., 2003). Also, substantial reductions of layer II of entorhinal-hippocampal projection neurons have been found not only in late AD, but also in subjects with MCI and early AD (Gomez-Isla, Price, McKeel, Morris, Growdon, & Hyman, 1996; Kordower, Chu, Stebbins, DeKosky, Cochran, Bennett, & Mufson, 2001; Price, Ko, Wade, Tsou, McKeel, & Morris, 2001). These findings lend further support to the hypothesis that neuropathology-related disruption of the perforant pathway initiates a compensatory cholinergic sprouting response in the medial septal/lateral septal nuclei (Geddes, Monaghan, Cotman, Lott, Kim, & Chui, 1985; Hyman, Kromer, & Van Hoesen, 1987; Ikonomovic et al., 2003). A similar increase in ChAT activity was seen in the superior frontal cortex in an investigation by Dekosky and colleagues (2002), suggesting that cholinergic upregulation is possible in more than one brain area in people with MCI. Thus, in conceptualizing the phenomenon of cholinergic upregulation as a compensatory response to disconnection between regions, it is possible that, in addition to affecting the perforant path, connectivity abnormalities may also involve prefrontal regions. Indeed, evidence for reciprocal connections from the dorsolateral prefrontal cortex (BA 9) to the hippocampus have been shown using tracing methods in the primate brain (Goldman-Rakic, Selemon, & Schwartz, 1984). Also, findings from primate studies provide evidence for a circuit linking the medial/lateral septal nuclei to the hippocampus (Mesulam, Mufson, Wainer, & Levey, 1983; Mesulam, Van Hoesen, Pandya, & Geschwind, 1977). These results indicate that approximately half of the cells in the medial/lateral septal nuclei are cholinergic (in the rat, but fewer in primates and humans).

Thus, functional connectivity abnormalities in AD are inferred not only from the extent of correlated signal fluctuations between various brain regions using different measures of physiologic signal (e.g. EEG and PET), but also from animal studies in which a lesion to an area known to be affected in AD results in decreased excitatory neurotransmitter innervation of another area. In view of this, similar connectivity abnormalities between anatomically-connected regions in AD patients should also be observable using FCMRI. Furthermore, drugs that increase cholinergic neurotransmission are hypothesized to improve connectivity among sites of neuropathology, such as the EC, the hippocampus, and the prefrontal cortex.

### 1.2.8 Neural networks underlying cognitive deficits in AD

#### 1.2.8.1 Episodic memory

A hallmark of AD is a deficit in episodic memory (Naugle, Cullum, & Bigler, 1998). Episodic memory deficits are often the earliest and most severe cognitive symptoms seen among AD patients (Desgranges, Eustache, Rioux, de La Sayette, & Lechevalier, 1996; Gainotti, Marra, Villa, Parlato, & Chiarotti, 1998). Lesion studies have shown that the left hippocampus ( Milner, 1972) and the left prefrontal cortex are necessary for performance of verbal auditory memory tasks ( Shimamura, Gershberg, Jurica, Mangels, & Knight, 1992; Zatorre & McEntee, 1983). It is traditionally recognized that key cognitive processes necessary for performance of episodic memory tasks include encoding, storage, and retrieval of information (Dolan & Fletcher, 1997), as well as language production (Fuster, 1989). These processes engage both the left inferior frontal gyrus, specifically BA 44 and BA 45

(Fuster, 1989), and the DLPFC ( Lepage, Beaudoin, Boulet, O'Brien, Marcantoni, Bourgouin, & Richer, 1999).

Additional processes necessary for performance of episodic memory tasks include semantic working memory (Fuster, 1989; Goldman-Rakic, 1987; Smith & Jonides, 1997) and semantic information processing (Craik & Lockhart, 1972). Working memory is necessary to maintain perceived information online, while new information is being processed by the listener. This ability to perform two tasks simultaneously may reflect the ability to switch between the information relevant for one or the other process (Fletcher & Henson, 2001). Individuals with frontal lesions may be disproportionately impaired on performance of dual tasks compared to single tasks (McDowell, Whyte, & D'Esposito, 1997). Consistent with these findings, evidence from functional neuroimaging research shows dorsolateral frontal activation during concurrent performance of two tasks, a spatial rotation task and a semantic judgment task (D'Esposito, Detre, Alsop, Shin, Atlas & Grossman, 1995). Thus, evidence from lesion studies and functional neuroimaging studies points to the role of the dorsolateral prefrontal cortex in switching, a cognitive process necessary for episodic memory performance.

It has similarly been shown that left BA 47 is responsible for the retrieval and/or selection of semantic knowledge (Duncan & Owen, 2000; Fiez, 1997; McDermott, Petersen, Watson, & Ojemann, 2003), implicating the IFG in functions important for performance of episodic memory tasks. Both processes have been associated with pathways linking the DLPFC and hippocampus (Goldman-Rakic, 1992).

Another cognitive process necessary for performance of episodic memory includes the ability to make inferences. For example, in the Logical Memory I task (Wechsler Memory Scale – Third Edition, WMS-III, Wechsler, 1997) it is necessary for the listener to infer that the characters in a story (Anna Thompson and her children) needed money, even though this was never explicitly stated in the story. Findings from functional neuroimaging studies show that the right DLPFC and right IFG are involved in making inferences in discourse (Mason & Just, 2004; Beeman, Bowden, & Gernsbacher, 2000), the same process that is posited to underlie performance of LM I.

Additional evidence from lesion studies and functional neuroimaging studies point to the role of right hemisphere functions in performance of episodic memory tasks. While left medial temporal lobe lesions can impair verbal memory (Milner, 1972; Hermann, Wyler, Richey, & Rea, 1987), right medial temporal lobe lesions can impair nonverbal memory (Kimura, 1963; Taylor, 1969). Consistent with findings from this research, functional neuroimaging studies show activations lateralized more to the left medial temporal lobe during encoding of words (Bernard, Desgranges, Platel, Baron, & Eustache, 2001; Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003), activations lateralized more to the right medial temporal lobe during encoding of less verbalizable material (e.g., patterns) (Golby et al., 2001), and bilateral activations during encoding of intermediately verbalizable material (e.g., scenes or nameable objects) (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Kelley, Miezin, McDermott, Buckner, Raichle, Cohen, et al., 1998 ). The episodic memory task used in this study, Logical Memory I, involves verbal information in the form of a story. Although it would be expected to enlist the left hippocampus in order to encode this verbal

material, it is likely that non-verbal encoding strategies are involved in performing this task (e.g., remembering the story through a visual scene). Thus, it is reasonable to suggest that the right hippocampus plays an important role in verbal tasks (Wilson, Isokawa-Akesson, Babb, & Crandall, 1990; D. Zaidel, 1995), including this one.

There is less evidence for lateralized prefrontal functions in the performance of material-specific episodic memory tasks from lesion studies (Hwang & Golby, 2006). However, some evidence suggests that the left prefrontal cortex may be more involved in encoding of information, and the right prefrontal cortex is thought to be more involved in retrieval (Lepage et al., 1999; cf. Hemispheric Encoding and Retrieval Assymetry [HERA] model of Tulving, Tulving Kapur, Markowitsch, Craik, Habib, & Houle, 1994; Sandrini, Miozzo, Cotelli, & Cappa, 2003). Indeed, findings from functional neuroimaging show that in addition to the left prefrontal cortical involvement, right BA 46, 9 and BA 44 are also recruited during performance of verbal episodic memory tasks (Lepage et al., 1999; cf. HERA model).

The medial septal nuclei are also known to be involved in memory-related functions. For example, studies in rats show that performance accuracy on spatial working memory tasks is correlated with single unit electrophysiological activity in this region after pharmacological manipulation or lesions to the area (Givens & Olton, 1990; Mizumori, McNaughton, & Barnes, 1989). As discussed earlier, the medial septal nuclei have reciprocal connections to the hippocampal formation in primates (Mesulam et al., 1983; Mesulam et al., 1977). There is further evidence for effects of the medial septal nuclei on theta wave frequency bands of EEG signal in the hippocampal formation (Lee, Chrobak, Sik,

Wiley, & Buzaki, 1994). One may therefore speculate that connectivity with the medial septal nuclei may affect not only memory in general, but also Logical Memory I in particular, possibly through perceptual selection (Zhou, Tamura, Kuriwaki, & Ono, 1999).

Thus, findings from lesion studies and functional neuroimaging studies indicate that the cognitive processes thought to underlie episodic memory tasks enlist bilateral IFG, bilateral DLPFC, bilateral hippocampi, and the medial septal nuclei. Because AD patients often show primary deficits in performance on episodic memory tasks, it is likely that dysfunction of these areas contribute to these symptoms. As mentioned above, known anatomical connections link the IFG to the DLPFC, hippocampus to IFG, and hippocampus to DLPFC in primates. Therefore, it is likely that dysfunction of one of these areas may contribute to disruption of functional connectivity among them.

#### 1.2.8.2 Verbal fluency

Verbal fluency tasks require subjects to generate as many words in a given time period satisfying certain criteria. A common version of the letter fluency task requires subjects to generate as many words as possible beginning with the letters 'F', 'A', and 'S' within one minute each (Spreen & Strauss, 1998). Patients with AD perform significantly worse than normal controls on letter fluency tasks (Chertkow & Bub, 1990; Hodges, Salmon, & Butters, 1990; Shuttleworth & Huber, 1988). Lesion experiments have shown that impaired letter fluency is associated with left frontal lobe dysfunction (Benton, 1968; Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981; Milner, 1964). There is agreement that effective letter fluency permance requires phonemic retrieval strategies (Crowe, 1992; Monsch, Bondi, Butters, Paulsen, Salmon, Brugger, & Swenson, 1994), which in turn engage

word-retrieval, phonological processing, and language production. These processes all engage the left inferior frontal gyrus, specifically BA 44 and BA 45 (Paulesu, Goldacre, Scifo, Cappa, Gilardi, Castiglioni, Perani, & Fazio, 1997; Phelps, Hyder, Blamire, & Shulman, 1997; Salthouse, 1988).

It has also been suggested that the left inferior frontal gyrus serves as a semantic working memory or semantic executive system, which accesses, maintains and manipulates semantic representations that are stored elsewhere (Gabrieli, Poldrack, & Desmond, 1998; Poldrack, Wagner, Prull, Desmond, Glover, & Gabrieli, 1999). The executive semantic system can provide an alternative strategy for generating words by sampling different semantic categories (Abrahams, Goldstein, Simmons, Brammer, Williams, Glampletro, & al., 2003). The part of the left inferior frontal gyrus that mediates the retrieval and/or selection of semantic knowledge is BA 47 (Duncan & Owen, 2000; Fiez, 1997; McDermott et al., 2003).

Other cognitive processes are required for performance of letter fluency. One of these is response selection (Passingham, 1995), thought to involve the left DLPFC (Gurd, Amunts, Weiss, Zafiris, Zilles, Marshall, & Fink, 2002; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). Another necessary component is switching between strategies (Estes, 1974; Laine, 1988; Troyer, Moscovitch, & Winocur, 1997), which again involves the left DLPFC (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Sohn, Ursu, Anderson, Stenger, & Carter, 2000). Retrieval strategies are also necessary to perform the task. Findings from lesion studies have demonstrated the importance of the hippocampus to retrieval strategies. For example, findings from a study on individuals with left temporal

lobe lesions showed impaired letter fluency performance (e.g., Jokeit et al., 1998). This is consistent with findings from fMRI studies showing both left (Fu et al., 2002) and right (Weiss et al., 2003) hippocampal activation during performance of letter fluency tasks. Considering the evidence from these three studies, as well the assumption that verbal fluency involves the hippocampus in lexical retrieval preceding word production, it is hypothesized that the hippocampus is involved in the verbal fluency network.

There is evidence of right hemisphere frontal involvement in this task as well. Findings from lesion studies have discovered impaired performance on letter fluency tasks among individuals with right frontal lesions (Baldo & Shimamura, 1998; Miller, 1984). Functional neuroimaging research shows engagement of the right DLPFC and right IFG in switching tasks (Berman et al., 1995; Fukuyama et al., 1997; Monchi et al., 2001; Nagahama et al., 1998, 1999, 2001).

Deficits in executive functioning may reflect damage to the prefrontal cortex. Therefore, based on the link between the cognitive processes underlying letter fluency and the prefrontal cortex, performance on letter fluency may be a reflection of executive dysfunction (Baddeley & Wilson, 1988). Findings from functional neuroimaging studies are consistent with this notion, showing that performance of letter fluency is associated with activation in Broca's area and DLPFC (Brodmann's areas 46 and 9) (Cabeza & Nyberg, 2000; Indefrey & Levelt, 2000; McGraw, Mathews, Wang, & Phillips, 2001).

Thus, an information processing rationale implicates the existence of a circuit between the IFG and the DLPFC. Indeed, primate studies revealed a complex network of anatomical pathways linking BA 46 and BA 9 with the inferior arcuate cortex, the primate

homologue of Broca's area (Barbas & Pandya, 1989; Petrides & Pandya, 2002). There are several anatomical pathways linking the hippocampus to the IFG. They include projections from the hippocampus to the entorhinal cortex, which is linked with the IFG (BA 47/12) in primates (Petrides & Pandya, 2002) as well as projections from the hippocampus to the anteromedial nucleus of thalamus (Carmichael and Price, 1995), which project to the contralateral prefrontal cortex (e.g., orbito-medial prefrontal cortex) (Preuss, et al., 1987; Carmichael and Price, 1995).

In sum, findings from functional neuroimaging and brain lesion research suggest that the cognitive processes assumed to underlie letter fluency recruit the functions of the left and right IFG, the left and right DLPFC, and perhaps the hippocampus to perform the letter fluency task. AD patients consistently show impairments in letter fluency, and it is likely that dysfunction of these areas underlies these impairments. The sample of AD patients participating here demonstrated a significant improvement on the letter fluency task after donepezil treatment relative to baseline (McColl et al., unpublished manuscript). Known anatomical connections link the IFG and the DLPFC, hippocampus and IFG, and hippocampus and DLPFC. Thus, it is likely that dysfunction of one or both of these areas may contribute to disruption of functional connectivity among them. Hence, exploring functional connectivity among the hippocampus, IFG, and the DLPFC before and after donepezil treatment will add insight into the functional integrity of this putative network, how donepezil affects this circuit/network, and the relationship between change in connectivity of this circuit to change in letter fluency performance after donepezil treatment in an AD sample.

### 1.2.9 Hemispheric asymmetries in AD

#### 1.2.9.1 Relevance of intra- and interhemispheric relations

It is recognized that there are hemispheric asymmetries in anatomical, physiological, and behavior aspects of AD (Zahn, Juengling, Bubrowski, Jost, Dykierek, Talazko, & Huell, 2004; Ott, Heindel, Tan, & Noto, 2000; Massman & Doody, 1996). Some PET studies in AD show disproportionately higher metabolism in the left than the right hemisphere, while others show higher metabolism in the right than the left hemisphere (Huff, Becker, Belle, Nebes, Holland, & Boller, 1987). These metabolic patterns have been shown to be related to patterns of cognitive impairment, such that those with more metabolic deficits on the left show more impairment on verbal tasks, and those with more metabolic deficits on the right have more impairment on visuospatial tasks (Siegel, Shihabuddin, Buchsbaum, Starr, Haier, & Valladares Neto, 1996; Loewenstein, Barker, Chang, Apicella, Yoshii, Kothari, et al., 1989; Becker, Huff, Nebes, Holland, & Boller, 1988 ; Friedland, Budinger, Koss, & Ober, 1985).

It has been argued above that anatomical and functional disconnection play a central role in the profile of AD. This would suggest effects on interhemispheric connections among others. Such interhemispheric disconnection effects may be separated into homotopic connections, between homologous regions in the two hemispheres, and heterotopic connections, between non-homologous regions.

As already discussed, both verbal fluency and Logical Memory I may enlist both left and right hemisphere functions. Consequently, it is expected that performance on these tasks

will be affected by changes in the connectivity of both intrahemispheric (ipsilateral) and interhemispheric (heterotopic contralateral) connections.

It is generally assumed that the majority of fibers of the corpus callosum are homotopic (Clarke, 2003), although some argue for an important role for heterotopic connections as well (Di Virgilio & Clarke, 1997). Many functional connectivity studies investigating these connections found strong functional connectivity between homologous regions (homotopic contralateral connections) of the motor, somatosensory or visual regions both at rest and during task performance (Bartels & Zeki, 2005). Further, there is evidence, using both behavior (e.g., dichotic listening tasks) (Dimond & Brouwers, 1976) and physiological monitoring (e.g., EEG, ERP) measures (Buresova & Bures, 1976; Giurgea & Moyersoons, 1972), that a cholinergic pharmacological agent, piracetam, increases interhemispheric communication in humans and animals. For example, in one study using single cell recordings in rats, one side of the prefrontal cortex was electrically stimulated, eliciting a response in the homologous region of the opposite hemisphere. After administration of piracetam, the amplitude of this response was increased (Okuyama & Aihara, 1988). Such effects are most likely mediated by the corpus callosum. Thus, certain connections examined in the present study involve pairs of homologous brain regions. Also, anatomical connections within a single hemisphere were also examined (e.g., left hippocampus to left DLPFC).

# 2 PURPOSE OF THE PRESENT STUDY AND HYPOTHESES

The two primary aims of this study were: 1) exploring the effect of donepezil on connectivity within neuro-functional networks in patients with AD, and 2) exploring the relationship between change in connectivity within a subset of these networks and change in performance on selected neuropsychological measures. Neuro-functional networks were chosen based on three types of neural abnormality in AD: (1) neurochemical, based on key areas of the cholinergic system thought to be dysfunctional in AD; (2) neuropathological, based on key sites of neuropathology in AD; and (3) neurocognitive, based on major areas of deficit in AD.

With respect to the neurochemical and neuropathological networks, the principal hypotheses were: 1) that functional connectivity within these networks will increase due to the drug; and 2) that the drug will have a selective effect on these networks relative to a control network, LPVC-RPVC. For the neurocognitive networks, the principal hypotheses were: 1) that functional connectivity within these networks will change significantly after the treatment; 2) the drug will have a selective effect on these networks relative to the control network; and 3) changes in connectivity in these networks after donepezil treatment will be correlated with change in performance on the associated cognitive tests.

It is important to distinguish between the hypotheses-driven analyses and empirically-driven, exploratory, analyses in the present study. The hypothesis-driven analyses test hypotheses about connectivity changes between pre-specified regions motivated a priori by established neurochemical, neuropathological, and behavior data. By contrast, the

exploratory analyses identify sites of significant changes in connectivity outside of these pre-specified regions.

## 2.1 NEUROCHEMICAL HYPOTHESIS (AND EPISODIC MEMORY CONNECTION)

1. Functional connectivity between the medial septal nuclei and the left and right hippocampus significantly increases after donepezil treatment.

2. Functional connectivity within this network increases significantly more than in a control network, LPVC-RPVC.

## 2.2 NEUROPATHOLOGY HYPOTHESES

1. Key sites of neuropathology in patients with mild AD are the hippocampus and DLPFC (BA 46, 9, 46/9). Functional connectivity of the following connections significantly increase after donepezil treatment: LHIPP-LDLPFC, RHIPP-RDLPFC, LHIPP-RDLPFC, RHIPP-LDLPFC, LHIPP-RHIPP, and LDLPFC-RDLPFC.

2. Functional connectivity in this network increases significantly more than in the control network.

## 2.3 NEUROCOGNITIVE HYPOTHESES

The AD patients in this study showed a significant improvement on letter fluency after donepezil treatment, while performance on episodic memory did not improve (McColl et al., unpublished manuscript). Because memory and verbal fluency deficits are hallmarks

of AD, and donepezil is thought to improve cognitive functioning in both domains, it is important to: 1) determine the effect of the drug on the networks involved in these cognitive tasks, and 2) to explore the relationship of change in these networks with change in behavior performance on these tasks after treatment. It is important to examine the relationship between changes in connectivity and changes in the associated behavior. The prediction is that the components of the two cognitive networks both increase in connectivity and their change in connectivity is related to the change in the associated behavior. These predictions apply to each of the region-pairs that make up the networks and to each of the connections within them. More specifically,

1. Functional connectivity in the sample of patients with mild AD significantly increases after donepezil treatment in the ipsilateral and contralateral (heterotopic and homotopic) connections linking the left and right inferior frontal gyrus (BA 44/45) and the left and right DLPFC (BA 46, 46/9, 9).

2. Change in functional connectivity are significantly correlated with change in performance on letter fluency and episodic memory.

3. After donepezil treatment, functional connectivity significantly increases between the ipsilateral and contralateral (heterotopic and homotopic) connections of the left and right hippocampus and the left and right inferior frontal gyrus (BA 44/45).

4. Changes in functional connectivity are significantly correlated with change in performance on letter fluency and Logical Memory I.

5. Functional connectivity of the ipsilateral and contralateral (heterotopic and homotopic) connections linking the left and right hippocampus and the left and right DLPFC (BA 46, 46/9, 9) increase.

6. Changes in functional connectivity are significantly correlated with change in performance on Logical Memory I after donepezil treatment.

7. After donepezil treatment, functional connectivity significantly increases between the medial septal nuclei and the left and right hippocampus, and this is significantly correlated with change in performance on Logical Memory I.

## 2.4 CONTROL NETWORK HYPOTHESIS

In order to control for a possible global effect of the drug, it would be helpful to demonstrate that the change in the experimental connection is greater than that of an appropriate control network. The control network should satisfy the following criteria: (1) it is unaffected in mild AD; (2) it is not affected by donepezil, or relatively less affected by donepezil, than the experimental connections; (3) its baseline connectivity is close to the average of the other experimental connections; and (4) it has direct anatomical connections.

1. Baseline connectivity of LPVC-RPVC is within the range (neither the highest nor the lowest) of all the experimental connections for either measure of coherence (See below).

2. After donepezil treatment, functional connectivity between homologous primary visual cortex regions (BA 17) does not change or changes less than the experimental connections.

# 3 METHODS

## 3.1 PARTICIPANTS

Patients were recruited from the Alzheimer's Disease Center and the Mildred Wyatt and Ivor P. Wold Center for Geriatric Care at the University of Texas Southwestern Medical Center, at Dallas. All subjects were diagnosed by a geriatrician, geriatric psychiatrist, or neurologist using standard criteria (i.e., deficit in at least two areas of cognitive functioning including memory and one of the following: aphasia, agnosia, apraxia or abstraction). Inclusion criteria for participation included a clinical diagnosis of probable AD; a Mini Mental State Exam score greater than or equal to 15; and adequate sight, hearing, and comprehension to participate in the MRI study and neuropsychological testing protocol. Subjects were excluded if they were already taking any medication that might alter cerebral function and/or cognition, including donepezil or phenothiazines. Patients with a pacemaker or significant amount of metal in the body were excluded due to the requirements of MRI scanning. All participants were also screened to rule out the presence of any neurological diseases other than AD, any condition that could chronically affect cognitive functioning, or any major concomitant psychopathology. Participants were 11 patients with mild AD (based on MMSE). There were 4 males and 7 females (mean age = 75.5 ± 7.4 [range=62 to 84]; mean education = 14.3 ± 2.5 [range=12 to 18]).

## 3.2 NEUROCOGNITIVE TESTING

Data for the present study were collected as part of a larger MRI investigation conducted at the University of Texas Southwestern Medical Center at Dallas. Participants in this investigation were also administered additional neuropsychological tests, but for the purposes of this study, only selected measures were included (i.e., letter fluency [FAS; Spreen & Strauss, 1998], and Logical Memory I [LM I] subtest from the Wechsler Memory Scale – Third Edition, [WMS-III; Wechsler, 1997]). Cholinesterase inhibition therapy was administered to patients in the form of donepezil (Aricept™), initiated at 5 mg daily for 28 days, and then increased to 10 mg daily for 28 days. Caregivers were enlisted to monitor daily usage and compliance was verified by pill count. Pfizer U.S. Pharmaceuticals provided Aricept™ as a gift to the investigators, but did not participate in or provide support for the conception, design, analysis or conduct of the study. MRI acquisitions and neuropsychological testing were conducted at baseline and following a total of eight weeks of therapy. All patients gave written informed consent to participate in this study. The complete experimental protocol and consent form was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

## 3.3 MRI DATA ACQUISITION

MR images were acquired on a General Electric Horizon LX NV/i 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI) using the standard GE quadrature birdcage RF head coil. In order to minimize large head motion, each subject's head was immobilized with tightly fitting foam padding and a head strap that was fastened across the

forehead. For the collection of fcMRI data, a time series of 100 echo-planar image (EPI) volumes was acquired at 16 axial slice locations through the whole brain while subjects were at rest. Echo-planar images were acquired with a single-shot gradient-recalled EPI pulse sequence (sequential slice acquisition; repetition time [TR] = 2000 ms; echo time [TE] = 45 ms; flip angle = 90º; matrix = 64x64; field of view [FOV] = 24 cm; slice thickness = 7 mm; slice-to-slice gap = 0.5 mm). High-resolution images of the entire brain (3D Spoiled Grass [SPGR] pulse sequence: TR = 30 ms; TE = 5 ms; flip angle = 45°; matrix = 256 x 256; FOV = 24 cm; slice thickness = 2.0 mm) were acquired during the same scan session for each subject.

## 3.4 MRI DATA ANALYSIS

### 3.4.1 Pre-processing

AFNI software (Cox, 1996) was used for the analysis of MRI data. As a first step, to correct for subject motion, a three-dimensional volume registration algorithm was applied to each EPI dataset. This program can effectively deal with movements that are less than 0.5-voxel displacements or 2º rotations. Two subjects showed motion that exceeded these criteria, respectively. In order to remove excessive signal values due to movement, such 'outliers' (i.e. signal greater than 3.5 times the standard deviation for the signal time course were replaced with the median value. The next step involved temporal filtering of the data. Previous work has demonstrated that it is the low-frequency components of time series MR signal data that show significant interregional correlations in functionally related brain areas (Biswal et al., 1995; Cordes, Haughton, Arfanakis, Carew, Turski, Moritz, Quigley, &

Meyerand, 2001). Thus, a low-pass filter was applied to the EPI data to remove all frequencies greater than 0.08 Hz.

### 3.4.2 Isolation of seed regions of interest

For each subject, 'seed' volumes were identified for one region within each connection. The first step in this procedure involved localizing and tracing each region for each connection for each subject with the assistance of brain atlases (Duvernoy et al., 1999, 2004; Mai et al., 2004; Ono, 1990), tracing protocols (Mega et al. (2002), Laboratory of Neuroimaging, UCLA [LONI] website), and relevant neuroanatomical articles and texts (Amunts et al., 1999; Cook et al., 1992; Defrance, 1976; Foundas et al., 2001; Petrides et al., 1999, 2000, 2002; Rademacher et al., 1992, 1993). These regions were defined and traced according to each individual subject's neuroanatomy represented on his or her high-resolution anatomical image in AFNI (See Figure 1 for pictures of seed areas). Then, each seed or target mask was resampled to match the lower resolution of the functional dataset (Li et al., 2002). This provided an objective procedure for defining masks of ROIs. The limits of these individual low-resolution masks corresponded to the location of the signal of interest, which, in turn were used as the functional datasets to be analyzed. This identification procedure was repeated for the right and left hemisphere for each subject. However, for small midline structures (i.e., medial septal nuclei), this procedure was done only once because the limited resolution of the functional data could not accommodate the tracing of meaningfully distinct masks for both homologous regions. A more detailed description of the procedure used to delineate these regions of interest is presented in the Appendix.

### 3.4.3 Identification of correlated regions

Next, the temporally filtered time series MR signal data were extracted from the voxels falling within the 'seed' volumes. Voxel data were averaged to create a single MR signal time course for each seed. Next, time courses were used as ideal reference functions for cross-correlation with temporal fluctuations in MR signal from all other brain voxels. For each subject, two indices of coherence (i.e. correlated signal change) were used. The first was the least-squares fit coefficient using the AFNI program 3dFIM+, and second, the z-score using the permutation test implemented in AFNI (Belmonte & Yurgelun-Todd, 2001), reflecting the rank of corresponding fit coefficient values relative to the other voxels in the brain. Maps of regions whose signal fluctuations were functionally coherent with the signal from the seed region were then created.

Target regions in each connection were identified and defined for each subject using the same technique as for the seed regions. For the primary analyses, the least-squares fit coefficient values across all voxels in the brain were calculated, and those that fell in a given target region were averaged. Then, the average fit coefficient was used to reflect the average magnitude of connectivity in a given target region of a given connection. In addition, significantly correlated voxels identified by z-scores ($p < 0.05$) within each target region were identified. For the exploratory analyses, coherence maps of the fit coefficient values in each voxel in the brain were created for each seed area.

### 3.4.4 Measuring change in functional coherence from Time 1 to Time 2

Change in functional coherence was operationally defined in two ways: (1) as the change in the average magnitude of coherence of voxels in a target region with a seed area from time

1 to time 2, and (2) the change in the spatial extent of significantly correlated voxels in a target region with a seed area. To determine overall magnitude of coherence, the average fit coefficient value of all voxels within a target region was calculated. Spatial extent of significantly correlated voxels was determined simply by counting the number of significantly correlated voxels in a target region and dividing by the total number of voxels in that region. Magnitude of change of spatial extent was determined by subtracting values at time 1 from the values at time 2. Following each individual subject analysis, these values were collected and imported into SPSS for group analyses.

## 3.5 GROUP ANALYSES

### 3.5.1 Hypotheses-driven analyses

In order to facilitate testing the experimental hypotheses, The effect of treatment on three types of connections were investigated, namely, those originating in the left vs. the right hemispheres (Origin), those linking regions within a hemisphere (ipsilateral) vs. between hemispheres (contralateral), and those that involve the three main region pairs (BROCA-DLPFC, HIPP-BROCA, HIPP-DLPFC). The connections MEDSEP-LHIPP, MEDSEP-RHIPP and LPVC-RPVC were only included in some of the ANOVAs because they do not include the same number of connections as in the region pairs. The LPVC-RPVC connection is included in ANOVAs #1 and #3, and the MEDSEP-LHIPP and MEDSEP-RHIPP connections are included in ANOVA #1 only (see below). The following are the independent factors in the three ANOVAs: ‘Connection’ (out of a total of 18), ‘Drug’ (pre, post treatment), ‘Region pair’ (BROCA-DLPFC, HIPP-BROCA, HIPP-DLPFC),

'Ipsi.contra' (ipsilateral, contralateral), 'Origin' (hemisphere) of connection (left, right). The first ANOVA was conducted in order to determine significant effects of treatment for each connection. In order to refine the analysis of drug on coherence, a second ANOVA was employed. It distinguished between drug effects on ipsilateral connections on the one hand, and contralateral heterotopic connections. on the other. This ANOVA focused on the same three region pairs as in the first ANOVA, but compared the effects of the drug on connectivity in intra- *and* inter-hemispheric connections. In order to further refine this analysis, a third ANOVA was used to assess the drug effect on coherence within the four homotopic contralateral connections investigated in this study. The ANOVAs were organized as follows:

ANOVA #1: Connection (18) x Drug (2)

ANOVA #2: Drug (2 levels: pre, post) x Region pair (3 levels: HIPP-DLPFC, HIPP-BROCA, BROCA-DLPFC) x Origin (2 levels: left, right) x Ipsi-Contra (2 levels: ipsilateral, contralateral)

ANOVA #3: Homotopic Contralateral Connection (4 levels: LDLPFC-RDLPFC, LBROCA-RBROCA, LPVC-RPVC, LHIPP-RHIPP

The dependent variables for this design were: 1) Average fit coefficient of all voxels of a target ROI for each connection (average connectivity with the seed area). The average fit coefficient represents both the correlation coefficient and the ratio of the standard deviation of the signal in the target region divided by the standard deviation of the signal in the seed region (amplitude amplification ratio), and 2) Percentage of significantly correlated

voxels in a 'target' ROI out of the total number of voxels in a target region for each connection (spatial extent of significant connectivity with the 'seed' area).

### 3.5.2 Empirically-driven/exploratory analyses

For the exploratory group analyses, all subjects' fit coefficient coherence maps were analyzed using the AFNI program 3dttest. For this group analysis, one paired-samples *t* test was performed for each seed region: medial septal nuclei, left and right hippocampus, left and right Broca's area, left and right DLPFC, and left PVC. These *t* tests were performed to determine on a voxel-by-voxel basis where the group measurements at time 1 were significantly different from the group measurements at time 2. The outputs from these *t* tests were then thresholded using a voxel-cluster-size method for rejecting false positive coherence.

The appropriate cluster-size for the threshold was determined using the AFNI program AlphaSim. This program was used to estimate the probability of false positive coherence over all voxels in a three-dimensional functional volume through Monte Carlo simulation of the processes of random image generation, spatial correlation of voxels, voxel intensity thresholding, masking and cluster identification. Using an iteration process, the program estimates the likelihood of obtaining clusters of different sizes given a specified individual voxel probability threshold (.025) by chance. Spatial correlation estimates were calculated from the group *t* maps using the AFNI program 3dFWHM.

The goal for the group analysis was to determine a cluster size that achieved an overall significance level of alpha <.05 given an individual voxel probability threshold of .025. AlphaSim reports the number of times out of 1000 iterations of randomly generated

images that a given cluster size is also the maximum cluster size. AlphaSim was performed on each group *t* map. The lowest cluster size that achieved an overall probability level of less than .05 was 6 voxels. Clusters that met or exceeded this criterion were considered sites of significant change in functional connectivity from time 1 to time 2.

After identification of significant clusters, the degree of overlap of these clusters with distinct Talairach regions (i.e. "cluster subcomponents") were reported. For each cluster, the cluster sub-components that met the following criteria were reported: 1) clusters that exceed 5 % overlap with a Talairach region; 2) a cluster sub-component exhibiting highest overlap with any Talairach-defined regions; and 3) a cluster sub-component that overlapped with a previously defined ROI. In some cases, the Talairach region reported to overlap with a given cluster subcomponent has a recognizable sub-region. For example, the inferior parietal lobule includes BA 40 as a sub-region. In these cases, overlap of both was listed.

## 3.6 RELATIONSHIP BETWEEN CHANGE IN CONNECTIVITY AMONG REGIONS OF INTEREST AND CHANGE IN COGNITIVE TEST PERFORMANCE

The analysis of the relationship between the change in connectivity and change in behavior was explored in two complementary ways: a correlational analysis and an ANOVA. For the correlational analysis, the change in coherence of the connections within the neurocognitive networks and the control network was correlated with the change in cognitive test performance (i.e. verbal fluency and LM I) (differrence between raw score at time 1 and raw score at time 2 for each subject). For the ANOVA, a between-subjects variable

(responders, non-responders) was used, which was created using a median-split to partition the subjects into responders and non-responders (i.e., those who showed more improvement on a given measure and those who showed less improvement or decline). The prediction is that there will be a Response * Drug interaction, such that connectivity among responders will increase more than non-responders for each relevant connection.

# 4 RESULTS

## 4.1 CHANGE IN BEHAVIOR

The average baseline MMSE scores of this sample was 24.6 ± 1.7 [range 21 to 27]. The default assumption is that performance on both tests will improve after treatment. Table 4 shows the scores for letter fluency and LM I before and after drug treatment. There was a significant improvement in letter fluency, $t(10) = 2.38$, $p = .038$, but no difference in Logical Memory, $t(10) = .09$, $p = .93$. These neuropsychological test scores were used to examine the relationship between connectivity change and behavior change.

## 4.2 OVERALL CHANGE IN CONNECTIVITY

All hypotheses predicted an increase in connectivity following treatment. Change in connectivity following donepezil treatment was analyzed using three analyses of variance (ANOVAs) for average fit coefficient (Avg. fit) and spatial extent (SE) separately. All three ANOVAs included Drug as an independent variable. Since the study focused on the effects of the drug on connectivity and its relationship to behavior, only the effects involving Drug were explored further.

### 4.2.1 Effect of treatment on all connections

A two-way repeated-measures analysis of variance (ANOVA) was carried out: Connection (18) x Drug (2).

#### 4.2.1.1 Average Fit

Means for each connection (pre and post) are listed in Table 5. For Average fit, there was a significant main effect of Connection, $F(17, 170) = 7.13$, $p < .0001$, meaning there were significant differences in coherence among the connections. There was a weak trend for an overall Connection * Drug interaction, $F(17, 170) = 1.52$, $p=.092$. Although the overall Connection * Drug interaction was not significant, the main effect of Drug on each connection was examined based on a priori predictions. For this analysis, only two connections showed a significant effect of the drug treatment; LHIPP-LDLPFC decreased significantly, $F(1, 10) = 6.637$, $p=.028$, while LDLPFC-RDLPFC, $F(1, 10) = 6.457$, $p = .029$ increased significantly after treatment. These connections are marked with asterisks in Table 5.

#### 4.2.1.2 Spatial Extent

There was a significant main effect of Connection, $F(17, 170) = 4.06$, $p < .0001$, reflecting significant differences in the extent of coherence among the connections. SE for each network did not change significantly after the drug treatment for any of the connections.

## 4.3 TESTS OF THE RELATIONSHIP BETWEEN CONNECTIVITY CHANGE AND BEHAVIOR CHANGE

### 4.3.1 Correlations between connectivity change and and behavior change

Behavior change scores (post-pre) were correlated with change in connectivity within the associated networks, using one-tailed Pearson correlations. The results are listed in Table 7. The following connections correlated significantly with behavior change. For Average fit, FAS: RHIPP-LBROCA, $p = .006$; and LHIPP-LBROCA, $p = .006$. For average fit, LM I:

LPVC-RPVC, p = .028; and LBROCA-RDLPFC, p = .006. For spatial extent, FAS, LBROCA-RDLPFC, p = .043, and LPVC-RPVC, p = .022. For spatial extent, LM I: RBROCA-RDLPFC, p = .003; RBROCA-LDLPFC, p = .026; and MEDSEP-LHIPP, p = .012.

### 4.3.2 Responders vs. non-responders

The relationship between connectivity change and behavior change was also explored via ANOVAs using a new between-subjects independent variable, Response. All four repeated-measures ANOVAs that were run to test the primary hypotheses were repeated with the addition of this between-subjects variable. These analyses were conducted for FAS and for LM I separately for each dependent variable. To differentiate responders from non-responders, a median-split was used: the cut-off raw score difference for FAS was 3 (6 responders, 5 non-responders), and for LM I it was 0 (5 responders, 6 non-responders). Only ANOVAs with significant effects will be reported, and only significant effects will be listed.

#### 4.3.2.1 Measuring the effect of treatment on all the connections

##### 4.3.2.1.1 Average Fit

For Average fit, no significant effects involving Response for FAS and LM I were observed.

##### 4.3.2.1.2 Spatial Extent

Means (pre and post) for the responders and non-responders for FAS are listed in Table 7. For Spatial Extent, there was a significant Drug * Response interaction for FAS, $F(1, 10) = 5.793$, $p = .039$. Figure 4 shows that the overall mean connectivity of the responders increased while overall connectivity of the non-responders decreased.

There was a significant Connection * Drug * Response (LM I) interaction, F (17, 170) = 1.727, p = .043, meaning that the change in connectivity due to the drug in some connections for responders was different from the change in connectivity of the same connections for non-responders. This three-way interaction for subsets (specific connections) of the networks will be explored further in the subsequent ANOVAs in the exploratory section below. Changes in coherence in all 18 connections for the responders and non-responders are shown in Figure 5.

In order to determine the difference between the effect of the drug on responders and non-responders, 2-way Drug x Response ANOVAs were conducted for each connection. For Average fit there was a significant Drug * Response (LM I) interaction for LPVC-RPVC (p = .008), and there were two trends: LHIPP-LBROCA (p = .054) (FAS), and RBROCA-LDLPFC, F (1, 10) = p=.086 (FAS). For Spatial Extent, there were four significant Drug * Response interactions: LBROCA-LDLPFC (FAS), F (1, 10) = 5.275, p = .047 (FAS), LPVC-RPVC, F (1, 10) = 5.07, p = .051 (FAS), LHIPP-LBROCA, F (1, 10) = 5.56, p = .043 (LM I), MEDSEP-LHIPP, F (1, 10) = 9.26, p = .014 (LM I).

## 4.4 TESTS OF PREDICTIONS

### 4.4.1 Control Connection hypothesis

The effect of Drug on LPVC-RPVC was not significant. Since LDLPFC-RDLPFC was the only connection that increased in connectivity following treatment, its change in connectivity was compared to change in connectivity of LPVC-RPVC. A paired-sample 1-tailed t-test revealed a significant difference for avg. fit, t (11)= 2.03, p = .03. There was no

main effect of Drug on the control connection for Avg. fit, F (1, 10) = .817, p=.387, or for SE, F (1, 10) =.979, p=.346. For SE, the baseline connectivity (0.254) was more than 2 standard deviations above the mean (.095). Consequently, LPVC-RPVC did not satisfy the criteria for serving as a control.

### 4.4.2 Neurochemical hypothesis

There was no significant main effect of Drug on the neurochemical networks, medial septal nuclei-left and right hippocampi using either Average fit or spatial extent.

### 4.4.3 Neuropathology hypothesis

Significant main effects of Drug on connections in the neuropathology network are designated with asterisks in Table 3. Using Average fit, functional connectivity of LDLPFC-RDLPFC significantly increased, while functional connectivity of LHIPP-LDLPFC decreased significantly. Functional connectivity of the remaining ipsilateral and contralateral (homotopic and heterotopic) connections within this network did not change significantly after donepezil treatment. None of the connections in this network increased in functional connectivity after treatment using spatial extent.

### 4.4.4 Neurocognitive hypotheses

Overall, using average fit, there was no change of connectivity in either the episodic memory network (p = .32) or the verbal fluency network (p = .15). Significant main effects for the neurocognitive connections are designated by asterisks in Table 3. Of the 15 connections that comprise the verbal fluency network (all connections except MEDSEP-LHIPP, MEDSEP-RHIPP, and LPVC-RPVC), the two that showed a significant change in connectivity, using average fit, were the ones that changed in the neuropathology network..

Similarly, of the 17 connections that comprise the episodic memory network (all connections but LPVC-RPVC), the same two connections showed a significant change following treatment using average fit. Overall, spatial extent, there was no change in connectivity in either the episodic memory network ($p = .824$) or the verbal fluency network ($p = .869$) , using spatial extent. Similarly, for spatial extent, there were no significant main effects of Drug for any connection in the verbal fluency and episodic memory networks.

In sum, there was no evidence for changes in connectivity in the connections associated with the neurochemical hypothesis. Of the connections associated with the neuropathology hypothesis and the neurocognitive hypothesis, only 2 changed in connectivity: LDLPFC-RDLPFC increased and LHIPP-LDLPFC decreased (Avg. fit).

## 4.5 CHANGES IN INTRA- AND INTERHEMISPHERIC CONNECTIONS OF THE MAIN REGION PAIRS

In order to explore the effects of treatment on the three region pairs, HIPP-DLPFC, HIPP-BROCA, and BROCA-DLPFC, as a function of ipsilateral and contralateral connections, a four-way repeated-measures ANOVA was conducted: Connection pair (HIPP-DLPFC, HIPP-BROCA, BROCA-DLPFC) x Drug (pre, post) x Origin (L, R) x Ipsi-contra (ipsilateral, contralateral). The ipsilateral connections are: LHIPP-LDLPFC, LHIPP-LBROCA, and LBROCA-LDLPFC, RHIPP-RDLPFC, RHIPP-RBROCA, and RBROCA-RDLPFC. The contralateral connections in the three region pairs are: LHIPP-RDLPFC, RHIPP-LDLPFC, LHIPP-RBROCA, RHIPP-LBROCA, LBROCA-RDLPFC, and RBROCA-LDLPFC.

### 4.5.1 Average Fit

Means (pre and post) of the three region pairs are listed in Table 6. For Average fit, there was a significant main effect of Network, F (2, 20) = 8.605, p = .002. There was also a significant Network * Drug interaction, F (2, 20) = 4.87, p = .019. Post hoc comparisons showed a significant interaction, Network (BROCA-DLPFC, HIPP-BROCA) * Drug, F (1, 10) =7.289, p =.022.

### 4.5.2 Spatial Extent

There was a significant Region pair * Drug interaction, F (3, 30) = 3.982, p = .035. Once again, the means for the region pair BROCA-DLPFC are higher than the other two region pairs.

## 4.6 CHANGES OF CONNECTIVITY IN THE HOMOTOPIC CONTRALATERAL CONNECTIONS

In order to analyze the relative effect of treatment on the four homotopic contralateral connections (LDLPFC-RDLPFC, LPVC-RPVC, LHIPP-RHIPP, and LBROCA-RBROCA), a two-way repeated-measures ANOVA was carried out: Connection x Drug (pre, post).

### 4.6.1 Average Fit

For Average fit, there was a significant main effect of Connection: F (3, 30) = 5.445, p = .004. There was a trend for Connection * Drug interaction, F (3, 30) = 2.898, p = .051 (Figure 3). Follow-up post-hoc comparisons showed a significant Connection (LDLPFC-RDLPFC, LBROCA-RBROCA) * Drug interaction, F (1, 10) = 10.341, p = .009.

### 4.6.2 Spatial Extent

For Spatial Extent, there was a significant main effect of Connection, $F(3, 30) = 3.119$, $p = .041$.

## 4.7 EMPIRICALLY DRIVEN/EXPLORATORY ANALYSES: THE CLUSTERS

In order to investigate changes in connectivity with each seed area and the rest of the brain, exploratory analyses were carried out. For each seed area, I report clusters of significant change in connectivity with the seed. For each cluster, I also report cluster sub-components defined by their overlap with distinct brain regions defined in Talairach space.

### 4.7.1 Change in connectivity with IFG (BA 44, BA 45)

For the left IFG seed (Table 9; Figure 6), there were four clusters of significant change. The largest cluster, with its peak t-value in the left subcallosal gyrus of the frontal lobe, spanned the bilateral prefrontal cortex, predominantly on the left. In the left hemisphere, this cluster extended into the superior and middle frontal gyri, as well as the anterior cingulate gyrus. It also extended into the basal ganglia, primarily the caudate nucleus, and into the lentiform nucleus to a lesser degree. This cluster also involved the left superior and middle temporal gyri.

The next largest cluster, with a peak t-value in the right superior temporal gyrus, extended into other right temporal lobe regions, including the parahippocampal gyrus. This cluster also extended into the insula. The third cluster was restricted to the right prefrontal cortex. It included the right superior, middle and medial frontal gyri. The fourth cluster involved right parietal regions, including the inferior and superior parietal lobules as well as the precuneus.

With respect to the right IFG (Table 10), there were two clusters of significant change in connectivity. The first spanned both hemispheres of the frontal lobe and included the cingulate gyrus, insula, and precentral gyrus. It also involved subcortical regions including the left thalamus and bilateral basal ganglia, primarily the caudate and lentiform nucleus. The second cluster was restricted to the left cerebellum, predominantly involving the cerebellar tonsil.

### 4.7.2 Change in connectivity with DLPFC

For the left DLPFC, there were four clusters of connectivity change, all with peak values in frontal regions (Table 11 and Figure 6). The first spanned right frontal, temporal, and parietal regions. Frontal regions included the insula and precentral gyrus, while in the temporal lobe, this cluster extended into the superior temporal gyrus. Parietal involvement included the inferior parietal lobule (BA 40) as well as the superior parietal lobule. The second cluster of connectivity change with the left DLPFC involved right prefrontal regions, including the superior frontal gyrus (BA 9 and BA 8), the medial frontal gyrus and the anterior cingulate gyrus (BA 32). The third cluster of connectivity change included the left temporal and parietal lobes. In particular, this cluster involved the superior temporal gyrus as well as the supramarginal gyrus, including BA 39 and BA 40. The fourth cluster was restricted mostly to left posterior frontal lobe regions, including the insula and precentral gyrus. It also extended into the left superior temporal gyrus.

For the right DLPFC seed (Table 12), there were three clusters of change in connectivity, with peak t-values centered in frontal, parietal and cerebellar regions, respectively. The first cluster spanned frontal and right parietal regions. These frontal lobe

regions included bilateral, but predominantly right, medial frontal gyrus and BA 6. Other prefrontal cortical regions involved the right IFG, including BA 44 and BA 45. It also extended into subcortical regions, specifically the thalamus bilaterally. The second cluster was restricted to the left hemisphere and involved primarily the inferior parietal lobule, including the supramarginal gyrus, and the superior temporal gyrus. The third cluster involved the left cerebellum, particularly the cerebellar tonsil.

### 4.7.3 Change in connectivity with hippocampus

For the left hippocampus seed, there was a single cluster of significant connectivity change involving right occipital lobe regions (Table 13). It had a peak t-value in the right lingual gyrus and extended into the middle and inferior occipital gyri (Figure 6).

For the right hippocampus (Table 14), there were two clusters of significant connectivity change. The first had a maximum t-value in the right cerebellar tonsil and involved the cerebellum bilaterally. The second cluster involved primarily left subcortical regions including the basal ganglia, particularly the lentiform nucleus and the nucleus accumbens. This cluster also extended into the left thalamus.

### 4.7.4 Change in connectivity with the medial septal nuclei

For the medial septal nuclei (Table 15 and Figure 6), there were two clusters of significant change. The first cluster was restricted to the right prefrontal cortex. It had a peak t-value in the middle frontal gyrus (BA 46), overlapped mostly with BA 46 and BA 9, and extended into the IFG (BA 45 and BA 44), as well as the insula. The second cluster was also restricted to the right frontal lobe, including predominantly the precentral gyrus (BA 6) and extending into the middle frontal gyrus.

### 4.7.5 Change in connectivity with left PVC

There were three clusters of change in connectivity with the left PVC (Table 16). The first had a peak t-value in the right anterior cerebellar hemisphere (lobule IV), and included bilateral cerebellar structures, predominantly the right anterior cerebellar hemisphere and the right cerebellar tonsil. The second cluster involved left occipital regions, including mainly the lingual gyrus, cuneus, and middle and inferior occipital gyri. The third cluster had a peak t-value in the fusiform gyrus and extended into the left precuneus

# 5 DISCUSSION

## 5.1 SPATIAL EXTENT (SE) VS. AVERAGE FIT (AVG. FIT)

The variables spatial extent and average fit coefficient were employed to assess functional connectivity. These variables are likely sensitive to different factors. The average fit coefficient is sensitive to the degree of correlation among regions, taking into account both the correlation coefficient and the amplitude of the time courses, while SE reflects the extent of neural tissue involved, without specifying the precise correlation of each voxel. Spatial extent corresponds to the number of significantly-correlated voxels, while Avg. fit corresponds to the magnitude of correlation of all voxels in a particular target region, not just the significant ones. Thus, SE represents part of a target region, whereas Avg. fit represents the whole region.

## 5.2 FINDINGS FROM THE HYPOTHESIS-DRIVEN ANALYSES

### 5.2.1 Changes in connectivity following treatment

The effect of donepezil on connectivity is highly selective, as coherence in the majority of connections did not change significantly for either dependent variable. However, within the context of the whole brain analyses, there were additional areas of significant change in connectivity with the same seed areas studied in the hypothesis driven analyses. Only two of 18 connections changed in coherence, both using Avg. fit, LDLPFC-RDLPFC increased significantly, while LHIPP-LDLPFC decreased significantly. In addition, there was a trend for an increase in connectivity between RBROCA and RDLPFC using SE ($p = .07$), and the connectivity of LHIPP-RBROCA showed a weak trend towards a decrease

using SE ($p = .093$). The selective increase in connectivity in the LDLPFC-RDLPFC connection is consistent with findings that cholinesterase inhibitors increase activation in prefrontal cortical regions (Rombouts et al., 2002; Saykin et al., 2004).

Connectivity of region pair BROCA-DLPFC stood out from the other two main region pairs, namely HIPP-BROCA and HIPP-DLPFC. It had by far the highest overall connectivity, (pre + post)/2, (Avg. fit). It also showed a selective relative increase in connectivity following treatment, in which BROCA-DLPFC increased whereas the other two decreased (SE). Changes in connectivity with left Broca's area (especially in the left hemisphere) were more frequently associated with changes in behavior than either DLPFC or the hippocampus. Two factors may account for the differential effect of treatment on these region pairs. First, donepezil may have its greatest effects on connectivity of region pairs that are less affected by the disease, in this case BROCA-DLPFC. Second, in this study I focused on networks associated with verbal tasks, letter fluency and episodic memory. Consequently, there was a bias towards findings of relationships between behavior change and connectivity change in left Broca's area, which is a prominent linguistic structure.

*Control connection hypothesis:* Though connectivity in the control network did not change significantly after treatment, the data reveal that the choice of the connection between the left and right primary visual cortices as a control network may have been inappropriate. The primary visual cortex connection actually showed one of the greatest drug effects (fourth highest for Avg. fit, and highest for SE). Since the control was intended to reflect the non-specific effect of the drug, it was expected that it would change less than the experimental networks. Its failure to do so suggests that it was not a proper control. Furthermore, recent

data describe cholinergic marker deficiencies in this region in mildly impaired AD patients relative to normal controls and MCI patients (Ikonomovic et al., 2003). The control connection is meant to be an area not affected by the disease process in mild AD. Thus, the effect of the drug on a given experimental connection was assessed directly rather than via an interaction with the primary visual cortex.

*Neurochemical hypothesis:* The neurochemical hypothesis predicted that the coherence between the medial septal nuclei and the left and right hippocampi would improve after treatment. This was not supported for either dependent variable.

*Neuropathology hypothesis:* Of the six connections that comprise the neuropathology hypothesis, two connections showed a significant main effect of the drug: LDLPFC-RDLPFC, which showed an increase, and LHIPP-LDLPFC, which showed a decrease. The increase in connectivity of the connection LDLPFC-RDLPFC, a region thought often to have NFTs and NPs in AD (Cras et al., 1995; Giannakopoulos et al., 2003; Gomez-Isla et al., 1997), supports the claim that donepezil impacts areas with neuropathology in AD (Svensson & Giacobini, 2000; Sadot et al., 1996).

The effect of the drug on these two connections may be mediated by its effects on the neuropathology in the nodes, namely the DLPFC and hippocampus. The effect of the drug on these connections may be a function of the amount of (or degree of deterioration induced by) the neuropathology present in the nodes, such that the drug may increase connectivity between nodes with an amount less than a certain threshold, and have no effect on connectivity between the nodes (or one node) with an amount above a certain threshold. Thus, the increase in coherence of the LDLPFC-RDLPFC connection may be explained by

the dearth of neuropathology there or the relatively low amounts of uncompromised neurons there. Thus, the increase in connectivity of the LDLPFC-RDLPFC connection may reflect that the amount of neuropathology at either or both nodes is less than that threshold. On the other hand, if the amount of neuropathology in the node (or nodes) of a given connection exceed that threshold, then the drug should have no effect there. Because there was a significant decrease in connectivity in the connection LHIPP-LDLPFC rather than no change, this explanation of the effect of the drug there is incomplete. It is possible that the decrease is a consequence of the shift of resources from a region high in neuropathology, low in functional capacity, and in turn, low in functional demand (i.e. hippocampus) to a region low in neuropathology high in functional capacity, and in turn, high in demand (DLPFC).

*Neurocognitive hypotheses:* Neither network showed a change in overall connectivity. This suggests that change in connectivity of the episodic memory and verbal fluency networks do not parallel the change in the behavior in LM I and FAS, respectively. This suggests further that that the anatomical connections do not correspond very well to the behavior, either because the chosen ROIs were too few to accurately characterize the network, or too gross to represent the specific sub-regions responsible for the behavior.

Connections involving the hippocampus, Broca's area (and its right hemisphere homologue), and DLPFC in both hemispheres comprised the verbal fluency network. It was expected that the episodic memory network would increase in connectivity, because previous studies have shown improvement on memory tasks following donepezil treatment. By the same token, it was expected that connectivity in the verbal fluency network would increase, because donepezil has been shown to have a positive effect on performance of the FAS task.

The two connections that showed a significant change in connectivity, namely LDLPFC-RDLPFC and LHIPP-LDLPFC, are parts of both networks. These findings suggest that there is partial support for the hypothesis that these networks are affected by the drug.

### 5.2.2 Connectivity change vs. behavior change

#### 5.2.2.1 Correlations

*Control connection*: The increase in connectivity of the connection LPVC-RPVC appeared to have a negative relationship to LM I change (a decline) using Avg. fit and a positive relationship to FAS change (an increase) using SE. The same relationships between connectivity and behavior test performance that was true for LBROCA-RDLPFC is also true for LPVC-RPVC, namely a negative correlation between connectivity change and LM I change for Avg. fit, and a positive correlation between connectivity and FAS for SE. It seems that this connection supports the circuits that are important for FAS, but interferes with circuits supporting LM I. In this way, when the drug increases connectivity in this connection, it may associated with an improvement in FAS performance and a decline in LM I performance.

*Neurochemical connections*: An increase in coherence in the connections MEDSEP-LHIPP and MEDSEP-RHIPP was positively correlated with improvement in performance on LM I using SE but not Avg. fit. This suggests that change in connectivity among two regions thought to be important for performance of memory tasks is related to change in performance of LM I. This finding is consistent with previous pharmacological and lesion studies suggesting that this circuit links the medial septal nuclei and the hippocampus during memory tasks (Givens et al., 1990; Mizumori et al., 1989).

*Neurocognitive connections:* Even though some of these connections showed changes in coherence, it did not follow that the changes were associated with changes in behavior. Conversely, there were several connections that showed a significant correlation between connectivity change and behavior change (see below), but which did not show changes in connectivity following treatment.

An unanswered question in brain imaging research is whether a larger spatial extent corresponds to improved function. An increase in the number of significantly connected neurons indicates greater interaction between regions, although well connected interactions may take place within smaller subregions. The reason is that more skillful and efficient cognitive processing may actually recruit fewer neurons (Poldrack et al., 1999).

Inspection of Table 7 raises several important considerations. Some correlations were significant for some connections even though there was no main effect of Drug for those connections. When looking at each behavior and dependent variable separately, only a small minority of them were significantly correlated. On average, correlations between connectivity change and behavior change was more often associated with spatial extent than with avg. fit coefficient. In sum, only a small minority of connections showed a correlation with a behavior, and even fewer showed a significant drug effect. Of the connections that changed in connectivity in relation to change in behavior a majority involved Broca's area or its right hemisphere homologue. Broca's area may therefore be considered central to the effect of the drug on the relationship of connectivity and behavior among the connections explored in hypotheses-driven analyses. It is also notable that two connections, namely LBROCA-RDDLPFC and LPVC-RPVC, correlated with each behavior, albeit with different

dependent variables. These connections may be considered necessary to the performance of these cognitive tasks.

Even though most connections sampled were hypothesized to subserve both behavior measures, few of the connections showed a relationship with both behaviors, and when they did, they often showed correlations in opposite directions.

Significant coherence of a given connection may reflect a facilitatory or an inhibitory relationship between two nodes (Buchel & Friston, 2000). Thus, a significant correlation between two nodes of a circuit may reflect an inhibitory effect via the following two mechanisms. First, an inhibitory node of origin may directly inhibit the target node. Second, the node of origin may facilitate an intermediate inhibitory node, which in turn inhibits the target node.

It is important to note that the MRI data were not collected during performance of the LM I or FAS tasks. Instead, the data reflect the functional relationships among regions that can work together to perform cognitive tasks, such as FAS and LM I. If the degree of functional connectivity between two areas during the resting state reflects the degree to which they are functionally related, and if the degree of functional relatedness is a prerequisite for optimized cognitive processing, then functional connectivity may be an indicator of how well these functions will be performed. Thus, inferences may still be made about the relationship between functional connectivity and associated behaviors.

Of particular interest, there was a negative correlation between a change in connectivity in LBROCA-RDLPFC and change in LM I performance using Avg. fit, while there was a positive correlation between the change in coherence of this connection and

change in FAS performance using SE. This dissociation has implications for the differential effects of treatment on the two behavior measures, on the one hand, and the two measures of connectivity (Avg. fit and SE), on the other.

The negative correlation between change in connectivity of LBROCA-RDLPFC using Avg. fit and change in performance of LM I suggests an inhibitory effect. Conversely, the positive correlation between the change in connectivity of LBROCA-RDLPFC using SE and change in performance using FAS suggests a facilitatory effect. It can be argued both effects are possible, so that LBROCA-RDLPFC may simultaneously exert both a facilitatory and an inhibitory effect. For example, if the neurons represented by SE are mostly facilitatory, and if at the same time, the neurons represented by Avg. fit (minus those represented by SE) are mostly inhibitory, then an increase in connectivity using avg. fit can be associated with a decrease in behavior. Conversely, a decrease in connectivity using SE can be associated with an increase in behavior.

The positive correlation between change in RBROCA-RDLPFC and changes in LM I highlights the importance of right hemisphere prefrontal cortical regions for memory tasks. In particular, right prefrontal cortical functions are thought to be important for retrieval and for making inferences, both involved in LM I. This conclusion is consistent with functional neuroimaging studies showing right hemisphere activation during performance of episodic memory tasks (Lepage et al., 1999; cf. HERA model). It is also consistent with studies that show right prefrontal cortical involvement in making inferences in discourse (Mason & Just, 2004; Beeman et al., 1998). Further, the positive correlation between connectivity change in RBROCA-LDLPFC (SE) and LM I performance change points to the importance of

interhemispheric prefrontal cortical communication for the performance of LM I. This is especially true with respect to the cooperation of areas involved in retrieval of information and in making inferences (RDLPFC and RBROCA) and areas involved in encoding and in switching (LDLPFC). The positive correlation between change in coherence in the connection MEDSEP-LHIPP (SE) and LM I performance is consistent with findings that demonstrate the importance of this connection for memory-related tasks (Givens et al., 1990; Mizumori et al., 1989).

#### 5.2.2.2 ANOVAs (Responders/non-responders)

Although there was no overall main effect of drug on connectivity, as defined by SE, there was a significant Response x Drug interaction, such that connectivity increased for responders and decreased for non-responders (FAS). Similarly, although there was no overall significant Connection * Drug interaction for SE, there was a significant Response x Connection x Drug (LM I) interaction. However, for Average fit, there were no corresponding significant interactions with Response. Thus, SE differentiated the effect of the drug on connectivity changes , whereas Avg. fit did not. Similarly, LM I differentiated the effect of the drug, whereas FAS did not.

Although it is expected that responders increased in overall connectivity and non-responders decreased in connectivity after treatment, surprisingly, some connections actually show a decrease in connectivity following treatment in responders. More specifically, for SE, the ipsilateral connections (LHIPP-LBROCA and RHIPP-RBROCA) of the region pair HIPP-BROCA exhibited a relative decrease in connectivity following treatment in responders, but they showed a relative increase in non-responders. It may be speculated that

in responders a strategic process is facilitated which compensates for the malfunctioning hippocampal-prefrontal connection measured in this study, while other hippocampal connections necessary for memory remain functional.

Of the nine connections that showed a correlation between change in connectivity and change in behavior, only three showed the corresponding Connection x Drug x Response interactions, namely LPVC-RPVC (Avg. fit) for LM I; LPVC-RPVC (SE) for FAS; LHIPP-LBROCA (Avg. fit) for FAS; and MEDSEP-LHIPP (SE) for LM I. Further, even when connectivity did not change following treatment nor correlate with behavior, it was possible for the change in connectivity in responders to be different from that of non-responders, so that connectivity may be related to the behavior after all. Indeed, of the eight connections that did not correlate with behavior, two connections showed a Drug x Response interaction for that connection: LHIPP-LBROCA (SE) for LM I, and LBROCA-LDLPFC (SE) for FAS.

Some connections did not show an overall change in connectivity, nor did they show a relationship between change in connectivity (SE or Avg. fit) and change in behavior (FAS or LM I), nor did they show an interaction of Drug x Response. These connections included RHIPP-LDLPFC, LHIPP-RDLPFC, RHIPP-RDLPFC, RHIPP-RBROCA, MEDSEP-RHIPP, LBROCA-RBROCA, and LHIPP-RHIPP. It is noteworthy that with one exception (LBROCA-RBROCA) all of these connections involve the hippocampus. This suggests that the effect of the drug on the hippocampus may be weakest, possibly due to the overwhelmingly depressed state of hippocampal neurons before treatment in these patients (Allen et al., 2003; Li et al., 2002). Similarly, of the four interhemispheric homotopic connections that were sampled, the LBROCA-RBROCA connection was the one that showed

the greatest decline in connectivity following treatment. On the surface, this seems surprising in light of the pivotal role of Broca's area in the relationship between connectivity change and behavior change. However, coherence change in this connection did not show a relationship with behavior change (correlation with behavior nor Drug * Response interaction). This suggests that the relative decline in this particular prefrontal connection due to the drug is not related to the behaviors measured in this study.

### 5.2.3 Relative effect of drug on the three main region pairs

#### 5.2.3.1 Ipsilateral and heterotopic contralateral connections

The present study focused on three main region pairs, namely HIPP-DLPFC, HIPP-BROCA, and BROCA-DLPFC. The network BROCA-DLPFC stands out from region pairs HIPP-BROCA and HIPP-DLPFC; it had the highest overall connectivity, (pre + post)/2 (Avg. fit), and it showed a relative increase in connectivity following treatment, whereas the others showed a relative decrease (SE). The fact that donepezil had a relatively stronger influence on connectivity in the DLPFC than in other regions highlights its selective effect on attentional networks. This is also consistent with the idea that AChE inhibitors improve attention, and that the DLPFC is involved in attention.

#### 5.2.3.2 Homotopic contralateral connections

Donepezil treatment had dramatically different effects on the connectivity of the different "channels" of the corpus callosum. The fact that the LDLPFC-RDLPFC connection was the only one to show a significant increase in connectivity relative to the other "channels" considered in hypotheses-driven analysis points to the selective effect of the drug on the dorsolateral prefrontal cortex. This is consistent with studies showing that

administration of piracetam, a putative nootropic agent (i.e. cognitive enhancer), which is also thought to influence cholinergic neurotransmission, increases interhemispheric transfer in humans (Dimond et al., 1979) and in animals (Buresova & Bures, 1976), in general, as well as between the left and right prefrontal cortices in animals (Okuyama & Aihara, 1988), in particular. The finding that connectivity of the callosal connection LBROCA-RBROCA, a region immediately bordering LDLPFC-RDLPFC, decreased the most, highlights the functional difference between the two prefrontal regions. Such proximity may facilitate a drug-triggered resource-shift from regions where oxygen saturation is high and demand is low to regions where oxygen saturation is low and demand is high (M. Weiner, personal communication). This argument is analogous to the one made above about putative shifts of resources from the hippocampus to prefrontal regions.

The dorsolateral prefrontal cortex is commonly thought to act as a central executive, which is a modality-free attentional control system that allocates attentional resources to the performance of other cognitive tasks (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986). Indeed, there is evidence that AChE inhibitors may improve cognitive functioning by increasing attentional functioning (Francis et al., 1999; Bohnen et al., 2005). This is consistent with the finding in this study showing an increase in connectivity in the right dorsolateral prefrontal cortex with medial septal nuclei.

Connectivity of the LHIPP-RHIPP interhemispheric connection decreased as well. More generally, connections involving the hippocampus tended to decrease in connectivity following treatment (Avg. fit and SE). This connection is not in close proximity to the

DLPFC, but often has the most significant amount of neuronal degeneration of all other brain regions in AD.

## 5.3 FINDINGS FROM THE EMPIRICALLY-DRIVEN ANALYSES: THE CLUSTERS

The exploratory analyses identified clusters of voxels throughout the brain that changed significantly in connectivity with the seed area following treatment. The exploratory analyses may be seen both as an exploration of other areas showing change in connectivity following treatment, and as a conservative validation of the connections hypothesized to change after treatment using the SE index.

In addition to bilateral DLPFC, the right inferior parietal lobule showed a significant increase in functional connectivity with left Broca's area after treatment. Connections linking the IFG with DLPFC, and IFG with inferior parietal lobule have been described in primates (Petrides & Pandya, 2002). The exploratory analysis of the left IFG seed shows increased connectivity with right hemisphere frontal, temporal and parietal areas. These changes may be associated with improved pragmatic functions and discourse processing (Soroker et al., 2004). The connectivity change between left IFG and inferior parietal lobule, and superior temporal gyrus form an action-recognition system mediated by mirror neurons which may serve social cognition (Iacoboni, 2005). The increased connectivity in bilateral DLPFC as well as with the anterior cingulate gyrus may support an interface between motivation/drive and action (personal communication, M. Iacoboni, April, 2006).

Another area represented in clusters of significant change with left Broca's area is the left caudate nucleus of the basal ganglia. Basal ganglia-prefrontal connections have been described in primates (Alexander, DeLong, & Strick, 1986). These areas are important for performance of verbal fluency (Troster, Woods, & Fields, 2003).

The right IFG showed an increase in connectivity with bilateral cingulate cortex. Again, this circuit may subserve motivation/drive-action interactions. Finally, the IFG showed increased connectivity with the cerebellum, and this may support motor learning among other functions (Tamada, Miyauchi, Imamizo, Yoshioka, & Kawato, 1999).

Both left and right DLPFC had increased connectivity with the left supramarginal gyrus. In light of the role of the DLPFC as a 'central executive' in Baddeley's model of working memory, which is thought to also recruit the "phonological loop", this finding points to the effect of the drug on these connections. It is notable that the drug increased the connectivity between the left DLPFC and right frontal regions.

The area of significant change with the left hippocampus was the right lingual gyrus in the occipital lobe. Animal lesion studies show that there are anatomical projections from the parahippocampal gyrus to the primary visual cortex (Burwell, Witter, & Amaral, 1995). The parahippocampal gyrus, in turn, has strong connections with the hippocampus. Findings from fMRI studies show activation in both regions during visual memory tasks, suggesting that this connection is important for encoding of visual information (Rombouts, Scheltens, Machielsen, Barkhof, Frank et al., 1999). A cluster of significant change with the right hippocampus was shown in the left basal ganglia and right cerebellar tonsil. The finding of change in connectivity in the basal ganglia is consistent with EEG research showing slow-

wave synchronized oscillations between the hippocampus and basal ganglia (Allers, Ruskin, Bergstrom, Freeman, Ghazi, Tierney et al, 2002), suggesting that there are functional relationships between these two regions.

It was remarkable that change in connectivity with the medial septal nuclei was restricted to right frontal regions, all the more interesting, because there are no known anatomical connections between these two areas.

As can be expected, the primary visual cortex increased in connectivity with other visual areas including the lingual, cerebellum, and fusiform gyri. These increased connections are likely to support visual perceptual processes, including the use of imagery in verbal fluency episodic memory and verbal fluency.

*Convergence* Of the eight seed regions explored, three connections overlapped with the predictions: LBROCA-LDLPFC, LBROCA-RDLPFC, and LDLPFC-RDLPFC. Significant change in coherence was found among several connections not predicted, namely: MEDSEP-RDLPFC and MEDSEP-RBROCA. All of these involve both ipsilateral and contralateral connections.

Both the hypotheses-driven analyses and the empirically-driven analyses show an increase in connectivity of the LDLPFC-RDLPFC connection. It is noteworthy that there was also a trend for a significant negative correlation ($r = -.492$, $p = .062$) between change in this connection and change in LM I performance.

Also, change in some of the connections that were significantly related to change in behavior in tests of the main hypotheses showed up in the exploratory analyses. In particular, an increase in connectivity in LBROCA-LDLPFC in the exploratory analyses was

found. Correspondingly, the primary analysis disclosed a significant interaction, Drug x Response for FAS performance for this connection using SE. These findings are consistent with lesion studies and functional neuroimaging studies showing involvement of left Broca's area in word-retrieval, phonological processing, and language production (Milner, 1964; Paulesu et al., 1997), processes that are required for performance of letter fluency tasks. These tasks also require effective switching strategies (Fletcher & Henson, 2001; Estes, 1974; Laine, 1988; Troyer et al., 1997), which enlist activation of the left DLPFC (D'Esposito, Detre, Alsop, Shin, Atlas & Grossman, 1995). This convergent finding from the exploratory and primary analyses points to a functional relationship between the LBROCA and LDLPFC regions, and highlights the importance of donepezil for increasing that relationship, and consequently for increasing performance on letter fluency.

An increase in coherence was also found in the connection LBROCA-RDLPFC. This finding points to the functional relationship between these two regions. There was also a positive relationship between change in coherence in this connection (SE) and change in FAS performance, as well as a negative correlation between coherence change (Avg. fit) and change in LM I performance. As discussed earlier, the positive correlation between FAS performance and an increase in coherence in this connection point to the functional relevance of these regions to letter fluency performance and the effect of donepezil treatment on this relationship. Indeed, evidence from lesion studies and functional neuroimaging studies implicates the right DLPFC in performance of letter fluency tasks (Baldo & Shimamura, 1998; Berman et al., 1995).

Interestingly, the exploratory analysis revealed a significant increase in connectivity of the right prefrontal cortex, including the DLPFC and Broca's area, with the medial septal nuclei. The increase in coherence in these connections, MEDSEP-RDLPFC and MEDSEP-RBROCA, may reflect the functional affinity of the medial septal nuclei to other parts of the limbic system, particularly the hippocampus, which in turn have projections to prefrontal cortical areas. This finding is consistent with functional neuroimaging studies showing an increase in frontal activation following AChE inhibitor treatment (AChE inhibitor treatment and functional connectivity studies section).

Involvement of medial septal nuclei with memory is consistent with findings from animal studies showing that single unit recordings in rats are correlated with performance accuracy on memory tasks after pharmacological manipulation or lesions to this region (Zhou et al., 1999; Givens & Olton, 1990). Further, findings from animal studies show that levels of cholinergic markers decrease in the hippocampus and in the neocortex after lesions to the medial septal nuclei (Kuhar, Sethy, Roth and Aghajanian, (1973). This implicates cholinergic pharmacological agents like donepezil in function of this region. Studies investigating levels of cholinergic markers in AD and in mild cognitive impairment (MCI) suggest that the medial septal nuclei play a role in influencing levels cholinergic markers in the hippocampus and superior frontal cortex (DeKosky, et al., 2002; (Geddes et al., 1985; Hyman et al., 1987; Ikonomovic et al., 2003). This effect of the medial septal nuclei on the right prefrontal cortex may be responsible for the observation, in the primary analysis, of a significant positive correlation between the change in connectivity (SE) between RBROCA and RDLPFC and the change in performance of LM I.

# 6 LIMITATIONS

## 6.1 PHARMACOLOGICAL EFFECTS

The BOLD response is thought to reflect local changes in oxygenated blood flow elicited by neuronal activity, though the exact relationship of the BOLD signal and the underlying neural activity is unclear (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). It is possible that donepezil has a local neural effect, but also a global, non-specific vascular and respiratory effect that could, in turn, affect the BOLD signal (Venneri et al., 2002). However, if the non-specific global effect is the same across the whole brain (Honey & Bullmore, 2004), then this effect should wash out when comparing pre to post conditions, leaving any remaining signal change attributable to the local neural response.

## 6.2 MEASURING CONNECTIVITY AT REST

Numerous studies have reported that correlated low frequency BOLD signal fluctuations in the resting state reflect the functional relatedness of brain regions (e.g., Biswal, Yetkin, Haughton, & Hyde, 1995). Interpreting the meaning of significantly correlated signal is in part driven by assumptions made about the functional relevance of the underlying signal. Because it is unclear what the individual in the scanner is doing cognitively while the data is collected, inferences about the meaning of the correlated signal may be limited. For example, the person may be engaging in self-reflection during the resting-state (Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001). It was also suggested that a "default-mode" network, which becomes less active during performance of

externally-cued tasks, is active during this state (Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001). The same default-mode network is said to be active during easy, passive sensory processing, but not during more demanding tasks. (Greicius, Krasnow, Reiss, & Menon, 2003).

In addition to the difficulties related to the functional nature of the underlying signal, interpretation is also limited by the extent to which the signal reflects a steady-state variable. If the cognitive state of an individual in the scanner changes one or more times during the scan, then the underlying significance of a correlation driven by the time points at the end of a signal time course may be different from those at the beginning.

Furthermore, inferences about the relationship between correlated signal change within regions and change in performance of the associated behavior must be limited by the fact that the neuropsychological test data are not collected concurrently with acquisition of the BOLD signal. If many cognitive processes are necessary to perform a given behavior (e.g., verbal fluency), then the cooperation of different brain regions, in different combinations, is necessary to subserve these processes. Thus, inferences about the relationship between connectivity in a given connection and the associated cognitive process are limited as well. Indeed, a correlated signal observed during performance of a task may reflect relationships that are task-specific, rather than central to the associated function (Greicius, et al., 2003).

## 6.3 INCOMPLETE SAMPLING OF CONNECTIONS AND BEHAVIORS

Another limitation on making inferences about the relationship between connectivity and behavior is the possibility that either of the behaviors explored in this study, LM I or letter fluency, enlists regions to perform the task that are not sampled here. Thus, a given connection may represent only a small fraction of the total possible variance of correlation with a given behavior. Conversely, limits on making inferences about the relationship between a neuropsychological function and the cortical circuits that underlie it are limited by the fact that the behavior measures (e.g., LM I) may not adequately sample that function (e.g., episodic memory).

## 6.4 CONTROLLING THE VARIABLES

Another problem involves the design of the study. This study did not have a placebo-control comparison group. In order to ensure that any effects of treatment are attributable to the treatment itself, it is necessary to have a placebo-control group of AD patients not receiving treatment. This study would have also benefitted from having a comparison group of age-matched, gender-matched, and education-matched normal controls receiving treatment.

The test-retest reproducibility of fMRI measures may be problematic. The use of a placebo-control group could have helped determine that reliability, and thereby serve as a baseline for the drug effect in the treatment group. Further, Moser, Teichtmeister, & Diemling (1996) point out that the reproducibility for % signal enhancement in a BOLD

fMRI study was better than size of activated area. This suggests that average fit may be a more reliable index of connectivity than spatial extent.

## 6.5 LIMITED/RESTRICTED MEANING OF COHERENCE

Limitations of the BOLD signal and the sampling rate of the signal may interfere with inferences made about the neural firing underlying that signal. Because the signal is sampled every two seconds, it is not possible to have a window into the micro (millisecond) changes that may occur, which could in turn better characterize the relationship between coherence and a given behavior. For example, if two areas are involved in different stages of processing of a given cognitive process, then a correlated signal between them may suggest that they are highly connected, when in fact, the time courses when measured on the order of milliseconds might not be correlated.

Furthermore, a positively correlated signal between two nodes of a connection may reflect either an inhibitory or an excitatory relationship (Friston et al., 1993). Correlated signals may reflect a direct or indirect relationship between two areas. Task-related decreases in fMRI activation have been observed (Gusnard, Akbudak, Shulman, & Raichle, 2001). It is possible that one or two intermediate areas not sampled are more related to node 1 of a given connection than is node 2. Hence, connectivity between two nodes of a connection may be mediated by a third area, which may maintain an inhibitory or facilitatory relationship between the two nodes (Sherman, 2005). It is thus possible that a negative correlation between change in connectivity and change in behavior found in this study may

similarly reflect the effect of an intermediate inhibitory node (Greicius, Krasnow, Reis, & Menon, 2002; Hampson et al., 2002).

## 6.6 CARDIAC AND RESPIRATORY CONFOUNDS

It is possible that cardiac and respiratory effects influence the degree of correlation between the signal in one region and the signal in another. For example, it is posited that resting-state temporal correlations reflect inter-hemispheric functional connectivity, but other explanations are possible. For example, there may be a similar mechanical response in the two hemispheres to cardiac and respiratory pulsations, or symmetry between the blood supply routes of homologous regions (Maldjian, 2001). Cordes et al. (2001) explored the contribution of low frequencies and physiological noise to resting-state cross-correlation maps using fcMRI and found that these functional connectivity maps depended predominantly on low-frequency fluctuations and little on respiratory and cardiac noise sources. Nonetheless, it is still possible that a "punch-through" effect occurs, such that the remnants of the higher cardiac (0.6-1.2 Hz) and respiratory frequencies (0.1-0.5 Hz), removed during the preprocessing stages, may be present and masked by the lower frequencies of interest. However, it has been shown that the cardiac contribution is reduced at long TRs (Li., 2001).

## 6.7 IMPRECISION OF DEFINING REGIONS OF INTEREST AND OVERLAP

There are several limitations introduced by the imprecision of ROI definition. First, due to intersubject variability in human brain anatomy and the fact that the ROIs in this study

are based on macroscopic morphological landmarks alone, rather than cytoarchitectonic boundaries, the method of region delineation was imperfect . Next, the inferences made about the overlap of clusters of significant change in connectivity with distinct Talairach regions is limited for several reasons. First, in order to identify clusters of significant change in connectivity across the group, it was necessary to shift each subject's functional data and structural images into a common coordinate space. This process introduced spatial distortion that may have created a mismatch between the location of signal within a given region before transformation and its location after the transformation.

## 6.8 LIMITED SAMPLE SIZE AND MULTIPLE COMPARISONS

First, the sample size of this study, n = 11, was limited. Consequently, The distribution of scores (connectivity and behavior) may not be normal. This may violate the assumptions of some of the parametric tests, namely Pearson r and ANOVA. Furthermore, significant correlations may be sensitive to individual scores, whose removal would potentially result in the loss of significance. Second, the data reported are the results from multiple comparisons. For example, the analysis of the relationship between connectivity change and behavior change involved 18 (connections) x 2 (measures of connectivity) x 2 (measures of behavior) = 72 separate correlations. This increases the chances of false positive outcomes. A standard approach to this problem would be to introduce a Bonferroni type correction factor (i.e., adjusting the significance threshold by the number of comparisons). This difficulty may be mitigated by a priori predictions.

# 7 EXTENSIONS AND FUTURE STUDIES

There are further analyses that can be performed on the data set available for the present study. The data set includes other behavior measures that could be correlated with coherence among additional cortical connections. These behavior measures include Digit Span Forward and the MMSE. An important region to consider in future studies exploring the relationship between connectivity and FAS is the temporal lobe. A similarly important region to consider in future studies is the inferior parietal lobule in relationship between connectivity and Digit Span Forward (DSF).

## 7.1 DIGIT SPAN FORWARD AND SUPRAMARGINAL GYRUS

One of the original hypotheses in this study concerned change in coherence between the supramarginal gyrus/inferior parietal lobule and changes in performance on Digit Span Forward (DSF). Some studies have shown impaired performance in AD patients relative to normal controls on this task (Belleville, Peretz, & Malenfant, 1996). In fact, the sample of AD patients in the present study demonstrated a significant improvement on DSF after donepezil treatment (McColl et al., unpublished manuscript). AD patients perform significantly worse than normal controls on memory span tasks (Spinnler, della Sala, Bandera, & Baddeley, 1988). Memory for a series of digits, as is required by digit span tests, involves the 'phonological loop'. It includes a phonological store and a subvocal rehearsal system. The 'phonological store' holds verbal information (Baddeley, 1984), while the 'subvocal rehearsal system' is responsible for refreshing this verbal information (e.g., telephone numbers) . Digit Span Forward is considered a measure of the functioning of the

'phonological loop' (i.e. short-term memory processes) (Cherry, Buckwalter, & Henderson, 2002).

Lesion studies and functional neuroimaging studies indicate that the 'phonological loop' is subserved by Broca's area (BA 44/45) (Baddeley, Lewis, & Vallar, 1984; Collette, Salmon, Van der Linden, Degueldre, & Franck, 1997; Salmon, Van der Linden, Collette, Delfiore, Maquet, Degueldre et al., 1996) and the left supramarginal gyrus (BA 40) (Shallice & Vallar, 1990; Collette et al., 1997; Paulesu, Frith, & Frackowiak, 1993; Salmon et al., 1996). It is said to interconnect the phonological buffer (Broca's area) with the short-term store (BA 40).

Preliminary results from the exploratory analysis support the prediction that there is a significant change in connectivity with Broca's area in the Talairach-defined supramarginal gyrus/inferior parietal lobule after donepezil treatment.

In order to explore the relationship between coherence between Broca's area and supramarginal gyrus on the one hand, and DSF on the other, it would be necessary to delineate the supramarginal gyrus, a difficult matter.

## 7.2 APATHY AND ANTERIOR CINGULATE-DORSOMEDIAL NUCLEUS OF THALAMUS CONNECTION

It is likely that cognitive deterioration in AD is partly attributable, both directly and indirectly, to a loss of cholinergic innervation. The lack of innervation directly disrupts the communication within neurocognitive networks (Mosconi et al., 2004). Cholinergic innervation partially influences connectivity within these networks, and cholinergic

deterioration often leads to apathy and amotivation (Cummings & Kaufer, 1996; Murillo, Mendoza, & Diaz, 1988). In sum, apathy and amotivation may affect cognitive functioning. Specifically, apathy has been associated with relatively more severe deficits on frontal lobe–related tasks in AD (Kuzis, Sabe, Tiberti, Dorrego, & Starkstein, 1999; Starkstein, Brandt, Bylsma, Peyser, Folstein, & Folstein, 1992). Of particular relevance to frontal-lobe cognitive functions explored in the present study, a SPECT investigation performed by Migneco et al. (2001) showed a correlation between apathy as measured by the Neuropsychiatric Inventory (NPI) in AD and in non-demented elderly patients and performance on letter fluency. Consequently, donepezil treatment may improve cognition directly by increasing cholinergic neurotransmission, and indirectly, by ameliorating apathy. Findings linking donepezil to the amelioration of apathy will be discussed later in this section.

As mentioned, apathy is characterized by a loss of initiation and motivation, decreased social engagement, emotional indifference, and failure to direct attention to novel or interesting aspects of the environment (Marin, 1991). It is the most commonly observed behavior change in Alzheimer's disease (Tekin & Cummings, 2002), affecting approximately 70% of patients in the mild-moderate stages (Landes, Sperry, Strauss, & Geldmacher, 2001; Mega, Cummings, Fiorello, & Gornbein, 1996) and over 90% of patients in the later stages (Robert, 2002). Although apathy is commonly mistaken for depression, it is distinct and identifiable in AD (Boyle & Malloy, 2004; Levy, Cummings, Fairbanks, Masterman, Miller, Craig, Paulsen, & Litvan, 1998). Depression can be distinguished from apathy on the basis of dysphoria (e.g., sadness, hopelessness, and guilt), which is usually absent in patients who exhibit apathy (Boyle & Malloy, 2004). Therefore, apathy reflects a syndrome of primary

motivational loss and diminished emotional responsivity, whereas depression reflects a primary mood disturbance (Boyle & Malloy, 2004). This symptom has been linked to a dysfunction of the anterior cingulate circuit.

The anterior cingulate circuit facilitates the intentional selection of environmental stimuli based on their internal relevance (Tekin & Cummings, 2002). Disruption of this circuit can therefore be expected to lead to deficits in tasks that depend on controlled attentional processes, such as switching word retrieval strategies in performance of letter fluency.

Although few studies have investigated treatments specifically aimed at reducing apathy in AD, some evidence suggests that AChE inhibitors, including metrifonate, physostigmine, tacrine and donepezil, are effective for ameliorating this neuropsychiatric symptom (Cummings & Kaufer, 1996; Kaufer, 1998; Mega, Masterman, O'Connor, Barclay, & Cummings, 1999). Mega and colleagues (1999) studied 86 mild to moderately impaired AD patients. They found that 41% of patients showed an improvement in neuropsychiatric functioning following treatment, whereas 28% worsened, and 31% remained the same. Among responders, apathy as measured by the Neurpsychiatric Inventory improved significantly from baseline.

In sum, findings from lesion studies, functional neuroimaging studies, and postmortem neuropathological work link apathy to dysfunction in the regions that comprise the putative anterior cingulate circuit. Known anatomical connections between these regions exist in primates. Therefore, it is likely that malfunction within one or more of these regions in AD patients may contribute to a disruption of functional connectivity between them.

Based on evidence suggesting that AChE inhibitors may ameliorate apathy in AD patients, it is hypothesized that donepezil will improve the integrity of the connections between the anterior cingulate and the dorsomedial thalamus. Thus, exploring functional connectivity between the anterior cingulate and the dorsomedial thalamus before and after donepezil treatment will add insight into the integrity of this putative circuit, clarify how donepezil affects this circuit/network, and reveal the relationship between change in connectivity of this circuit and change in cognitive performance after drug treatment in a sample AD patients.

## 7.3 NEGATIVE FIT COEFFICIENT AND NEGATIVE CORRELATION

The findings of a negative correlation between change in connectivity in some connections and change in the associated behavior highlight the importance of investigating negative correlations between signal in one region and signal in another. The assumptions of this study are that a positive correlation between signals reflects significant connectivity, while a negative correlation reflects noise and detracts from a positive correlation. Here, in the context of change in connectivity after treatment, a significant increase in connectivity may reflect: 1) an increase from a positive correlation to a more positive one; 2) a shift from a negative correlation to a positive correlation; or 3) an increase from a negative correlation to a less negative one. However, it is possible that a negative correlation may reflect an inhibitory relationship between signal at rest (Greicius et al., 2003; Hampson et al., 2002). This can be explored in a future study, in which both positive correlations as well as negative correlations are assumed to reflect significant connectivity. A significant increase in connectivity may reflect: 1) an increase from a positive correlation to a more positive one;

and 2) a decrease from a negative correlation to a more negative one. At the same time, a significant increase in negative connectivity may reflect a stronger inhibitory process, as may occur with a slow enough phase shift of two identical signals.

In a study performed by Greicius et al. (2003), areas that are part of a "default-mode network" showed a decrease in activation during task performance while areas that are important for task performance show an increase in activation. During the resting-state, these "default-mode network" areas were negatively correlated with areas that were later involved in task performance. Thus, in future studies, it would be important to consider separately increases in negative connectivity as well as increases in positive connectivity after treatment to fully appreciate the range of possible changes in coherence.

## 7.4 GLOBAL MEASURES OF BEHAVIOR

It is possible to consider other behavior measures collected on this sample of patients to better understand the relationship between connectivity change and behavior change. In particular, MMSE performance change can be correlated with connectivity change to assess the relationship between MMSE performance change due to the drug and connectivity change due to the drug. Similarly, a between-subjects variable Response for MMSE performance can be added to an ANOVA exploring the relationship between MMSE performance change and connectivity change. The MMSE score reflects global cognitive functioning. Thus, it would be interesting to use baseline connectivity to predict who will respond to treatment using MMSE.

## 7.5 VALIDATION PROCEDURES

### 7.5.1 A validation procedure for the exploratory analyses

A procedure may be employed to validate the approach taken in the present study to determine areas that show a significant change in coherence with a seed area after treatment. First, in order to determine areas of significant connectivity in a target region, the signal from a seed region is averaged, and then correlated with the signal in every voxel in the target region prior to treatment and following treatment. Then, a paired t-test is performed on every voxel in the given target region to assess the change in coherence from pre to post treatment. The degree of correlation of the signal in any given voxel, x, in a seed region should closely approximate the average signal of the voxels in that region (or should be relatively better correlated with the average signal in the seed than any voxel outside the seed region). If voxel x falls within the distinct Talairach region corresponding to the seed area itself, then it should show no change in coherence relative to the seed area. This is because the signal in a voxel that is a subset of the original seed region should be highly correlated with the average signal in that region whether before or after treatment. If the Talairach region corresponding to the seed area is found in the exploratory analyses to contain a substantial number of voxels that change in connectivity with the seed area, then the procedure may be flawed. In other words, the seed region (e.g., PVC) converted to Talairach space does not coincide with the Talairach-defined boundaries of the corresponding region (i.e., PVC). Of course, the absence of an overlap is necessary but not sufficient to validate the procedure.

### 7.5.2 Analysis of symmetry

A procedure that may be employed to validate the assumption that functional connectivity does not reflect directionality is to compare the steps of correlating the average signal of a seed region with a target region to the reverse steps, i.e., the average signal of the original target is correlated with the original seed. If the correlation between the signal in the seed region and signal in the target region is non-directional, then the values reflecting the degree of coherence in both "directions" should not differ.

## 7.6 ANOVAS COMPARING CHANGE IN CONNECTIVITY OF THE WEAKER AND STRONGER HEMISPHERE

AD is often initially localized to specific regions within one hemisphere (Cummings & Kaufer, 1996). Thus, it may be expected that differential degeneration in the two hemispheres of the AD patients in this sample. This may result in a differential hemispheric response to donepezil, and consequently, differential changes in connectivity. Thus, by including the 'more' and 'less' affected hemisphere as an independent variable, it may be possible to tease apart the effect of donepezil on high functioning (relatively intact) neurons from its effect on low-functioning (relatively less intact) neurons. Here, 'less affected' corresponds to the hemisphere that is more 'active' (i.e. average power of the signal) before the drug treatment and 'worse' corresponds to the hemisphere that is 'less active' (i.e. average power of the signal) before the drug treatment.

In the data set of the current study, the two behavior tasks that showed improvement after donepezil were verbal fluency and digit span. Both are verbal tasks, and are associated

with the left hemisphere. Therefore, it is expected that change in performance on these tasks is associated with change in connectivity in the left hemisphere. Consequently, it would be important to correlate separately the change in behavior with change in connectivity in the left and the right hemispheres. I hypothesize that the former will be higher than the latter due to the verbal nature of the task.

# 8 CONCLUSION

The present study is partly exploratory. The experimental sample was small, yielding weak statistical power, and many analyses were performed, increasing the probability of false positives. There was no control group of patients receiving placebo, or of normal subjects receiving the drug. Activation was measured at rest rather than during task performance. The definition of ROIs was imprecise due to individual differences in neuroanatomy and in the relationship of different anatomical structures to particular behaviors. Consequently, the conclusions of the present study should be interpreted with caution, and are best considered predictions for future experiments.

The empirically-driven/exploratory analyses of the present study revealed a rich distributed system of connections that increased in connectivity following treatment. This system reflects inherent anatomical connectivity and supports several functional systems. These include increased connectivity 1) among frontal regions bilaterally, 2) between frontal areas and superior temporal and inferior parietal cortices, supporting verbal working memory and sensory-motor integration, and 3) between left Broca's area and right hemisphere cortical regions, suggesting increased right hemisphere involvement following treatment. Overall, the whole-brain analyses demonstrated a concentration of increased coherence among frontal connections, and highlighted interhemispheric interactions.

Figure 7 summarizes the hypotheses-driven findings of the present study. The main conclusion is that the effect of the drug on connectivity change was selective. Only one of the connections

involved in the neurochemical, neuropathology, and neurocognitive networks increased in connectivity following treatment. These hypotheses were therefore not strongly supported. More specifically, of the 18 connections sampled, only two changed in connectivity: the LDLPFC-RDLPFC connection increased in connectivity as measured by the average fit coefficient, whereas LHIPP-LDLPFC decreased in connectivity as measured by the average fit coefficient. By contrast, none of the *connections* changed in connectivity as measured by spatial extent. Thus, the drug seemed to affect connectivity among sub-optimally functioning neurons, measured by average fit, more than among highly functioning ones as measured by spatial extent. Thus, coherence change was selective to specific connections and to specific measures of coherence.

Of the three main *region pairs*, the exclusively prefrontal network, BROCA-DLPFC, increased in connectivity, whereas the overall connectivity of the two hippocampal region pairs, HIPP-BROCA and HIPP-DLPFC, decreased in connectivity, whether using average fit or spatial extent. This extends selectivity of the effect of the drug on coherence change from the level of connections to the level of region pairs. Selectivity of the drug effect held also when considering a subset of all the connections, consisting of homotopic contralateral connections. In particular, connectivity increased selectively in the LDLPFC-RDLPFC connection. This suggests that donepezil may exert its effects through frontal modulation of attention, given the role of the prefrontal cortex in executive control. However, the selectivity observed in the hypotheses-driven analyses is mitigated by the findings of the empirically-driven analyses, which showed extensive changes in connectivity with the seed areas throughout the brain following treatment (see above).

In general, a majority of the specific predictions made about the relationship between connectivity change and behavior change were not supported. However, most of the significant correlations involved left Broca's area, as might be expected from the verbal nature of the tasks. Similarly, the left hippocampus was more involved than the right hippocampus. This is consistent with the view that the left hippocampus has predominant functional connections with left cortical areas, including language areas, rather than with the right hippocampus. By contrast, the DLPFC showed equal involvement on both sides (see figure 7), suggesting that the drug increased bilateral intergration between prefrontal regions. Moreover, hippocampal connections have mostly inhibitory relationships to behavior, indicating reduced performance with increased connectivity.

There was a remarkable duality in the relationship of changes in connectivity of the same connections to changes in episodic memory, on the one hand, and letter fluency, on the other. In several instances, change in connectivity measured by average fit was negatively correlated with change in letter fluency, whereas connectivity in the same connection, measured by spatial extent, was positively correlated with change in episodic memory. This suggests that different cell assemblies within the same region of a given connection may have different functional roles in the two behaviors. Moreover, connectivity measured by average fit seems to have mostly an inhibitory relationship to behavior, whereas connectivity measured by spatial extent seems to have mostly a facilitatory relationship to behavior. Thus, the inhibitory relationship seems to be mediated by suboptimal neurons, indexed by average fit, whereas the facilitatory relationship seems to be mediated by the highly functioning neurons, indexed by spatial extent. The duality is all the more remarkable,

because the “spatial extent cell assemblies” are a subset of the “average fit assemblies”, suggesting that these two types of assemblies have a differential involvement in the two behaviors.

The connection LPVC-RPVC showed surprisingly “many” and diverse relationships to behavior (both FAS and LM I). It is possible to speculate that these relationships reflect the effect of the drug on prefrontal-visual feedback loops that modulate perception with attention. Presumably, the drug increases connectivity between visual areas and prefrontal areas, a connection which was not measured in this study. This would permit attentional modulation of visual processes, particularly of interhemispheric transfer associated with the two behaviors.

The empirically-driven/exploratory results provided only partial confirmation of the hypotheses-driven results. This highlights two levels of distortion, introduced on the one hand by the variability in individual neuroanatomy, and on the other by Talairach normalization. It also highlights the methodological differences in the two approaches. Future studies should use the findings from the empirically-driven exploratory analyses as a rough guide to choosing ROIs for hypothesis-driven main experimental analyses like those conducted in the current study.

# TABLES

Table 1: Region pairs, their associated connections, and their abbreviations

| Region pair | Abbreviation | Connection | Abbreviation |
|---|---|---|---|
| Medial septal nuclei-hippocampus | MEDSEP-HIPP | MEDSEP-left HIPP | MEDSEP-LHIPP |
| | | MEDSEP-right HIPP | MEDSEP-RHIPP |
| Hippocampus-Broca's area | HIPP-BROCA | left HIPP-left BROCA | LHIPP-LBROCA |
| | | left HIPP-right BROCA | LHIPP-RBROCA |
| | | right HIPP-left BROCA | RHIPP-LBROCA |
| | | right HIPP-right BROCA | RHIPP-RBROCA |
| | | left HIPP-right HIPP | LHIPP-RHIPP |
| | | left BROCA-right BROCA | LBROCA-RBROCA |
| Hippocampus-dorsolateral prefrontal cortex | HIPP-DLPFC | left HIPP-left DLPFC | LHIPP-LDLPFC |
| | | left HIPP-right DLPFC | LHIPP-RDLPFC |
| | | right HIPP-left DLPFC | RHIPP-LDLPFC |
| | | right HIPP-right DLPFC | RHIPP-RDLPFC |
| | | left HIPP-right HIPP | LHIPP-RHIPP |
| | | left DLPFC-right DLPFC | LDLPFC-RDLPFC |
| Broca's area- dorsolateral prefrontal cortex | BROCA-DLPFC | left Broca-left DLPFC | LBROCA-LDLPFC |
| | | Left Broca-right DLPFC | LBROCA-RDLPFC |
| | | Right Broca-left DLPFC | RBROCA-LDLPFC |
| | | Right Broca-right DLPFC | RBROCA-RDLPFC |
| | | Left DLPFC-right DLPFC | LDLPFC-RDLPFC |
| | | Left primary visual cortex-right primary visual cortex | LPVC-RPVC |

Table 2a: Main findings from SPECT on effects of AChE inhibitors on rCBF in AD patients

| **Authors** | **Drug** | **Rx. group** | **Control** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Ceravolo et al., 2004 | donepezil or rivastigmine<br><br>Scans: baseline and after 4.3 mos. of rx. | 24 mild-mod. AD pts. who were favorable responders to AChE inhibitors. | none | ↑ R cingulate; R and L prefrontal (DLFC); dorsolateral parietal; and L and R temporal | N/A |
| Lojkowska, et al., 2003 | rivastigmine<br><br>Scans: baseline and after 12 mos. of rx. | 25 probable AD pts. | 8 AD and vascular dementia pts.-no rx | ↑ in all ROIs ranging from 103%-107% of baseline. | ↓ in all ROIs ranging from 82%-95% of baseline. |
| Venneri et al., 2002 | rivastigmine<br><br>Scans: baseline, 3 mos., and after 6 mos. of rx. | 16 mild AD pts. | 11 mild AD pts. | 12 responders/ 3 mos.: diffuse BL ↑ in DLFC, temporal and parietal regions; 6 mos.: pattern of ↑ uptake persisted, with largest. ↑ in medial frontal and ACG regions.<br><br>4 non-responders: at 3 mos.: ↓ in BL multifocal region in P frontal lobe and adjacent P-T cortex; 6 mos.: expansion of these areas. | 3 mos.: ↓ in BL temporal, limbic and F-P regions; 6 mos.: more extensive area of ↓ seen. |

| **Authors** | **Drug** | **Rx. group** | **Control** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Nobili et al., 2002 | donepezil<br><br>Scans: baseline and after 12 mos. of rx. | 25 mild AD pts. | 13 mild-mod. AD pts. – no rx | none | ↓ in L temporal lobe, especially mesial-temporal cortex and T-O junction;<br><br>No diff. in **Δ** between groups from time 1 to time 2. |
| Nakano et al., 2001 | donepezil<br><br>Scans: baseline and after 12 mos. of rx. | 15 AD pts. treated w/ donepezil. | 20 AD pts. treated w/ placebo | none | ↓ in the R and L ACG, R prefrontal cortex, R inferior parietal lobules, and R middle temporal gyrus relative to donepezil-treated pts. |
| Staff et al., 2000 | donepezil<br><br>Scans: 3±34 weeks before and 14±65 weeks after rx. | 11 mild-mod. AD pts. | none | global ↑; largest ↑ in frontal lobes<br><br>4 pts. showed global ↓ | N/A |

| **Authors** | **Drug** | **Rx. group** | **Control** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Blin et al., 1997 | physostigmine<br><br>Rx. interval=4.75 hours of infusion<br><br>2 Conditions: placebo; physostigmine infusions<br><br>2 Scans: for placebo and for drug | 10 mild-mod. AD pts. | 10 elderly normal controls;<br><br>10 young normal controls | No difference between groups in regional Δ<br><br>All subjects together: ↑ in rCBF in temporal cortex, occipital cortex, cerebellum, striatum, thalamus | N/A |
| Riekkinen et al., 1997 | tacrine, single dose; 1 scan after dose | 28 probable AD pts. (9 responders and 18 non-responders) | same pts. receiving placebo | Responders had ↑ values in L and R prefrontal and frontal areas relative to non-responders. | N/A |
| Harkins, et al., 1996 | tacrine<br><br>Scans: baseline and after 26.8 wks of rx. | 12 AD pts. | none | 7 pts. had ↑ in perfusion at follow-up.<br><br>5 pts. had ↓ in perfusion at follow-up<br><br>(no p-values provided) | N/A |

| **Authors** | **Drug** | **Rx. group** | **Control** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Minthon, et al., 1993 | tacrine; rx. interval=6 weeks for each condition;<br><br>conditions: placebo+placebo; placebo+tacrine; and tacrine+lecithin;<br><br>4 scans: at pre-rx. and after each rx period | 17 probable AD pts.; all pts. went through each rx. condition | Same pts. receiving placebo condition | All pts: no hemispheric differences found or rCBF between each rx.<br><br>Responders (6): 2.3 ↑ in L P temporal region from placebo to rx condition | N/A |
| Ebmeier, et al., 1992 | velnacrine, single dose | 11 AD pts. | 10 AD pts. receiving placebo | ↑ in relative mean rCBF selectively in superior frontal regions relative to placebo rx pts.<br><br>↓ in relative mean rCBF selectively in L P-T region relative to placebo rx pts. | N/A |

| Authors | Drug | Rx group | Control | Significant Δ in Rx group | Significant Δ in control group |
|---|---|---|---|---|---|
| Cohen, et al., 1991 | tacrine;<br><br>Scans: AD pts. received drug and had scan at baseline and after 2 wks of rx.;<br><br>controls: no drug and scan at baseline | 6 probable AD pts. | 5 normal elderly subjects (did not receive drug; only had baseline scan) | No difference between mean CBF or rCBF in any region between scans.<br><br>(p-values not provided) | N/A |
| Hunter, et al., 1991 | physostigmine<br><br>Scans: after saline infusion and 1 wk. later after drug infusion | 7 pre-senile probable AD pts. | Same 7 pts. on placebo | ↑ in values reported with respect to % change in asymmetry:<br>↑ in left vs. right frontal and left "high" frontal regions.<br><br>↑ in left vs. right F-P regions | N/A |
| Tune et al., 1991 | physostigmine<br><br>Rx.: drug infusion<br><br>2 scans: at baseline and after 30 min. of infusion | 6 AD pts. (ranging from mild-mod.) receiving drug | none | (p-values not provided)<br><br>↑ CBF in most pts.↑ among ROIs | N/A |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Geaney et al., 1990 | physostigmine<br><br>2 scans: both AD pts. and normal controls had scan after single dose of saline and a week later after single dose of drug. | 8 AD patients | 8 normal elderly controls | ↑ rCBF after rx in left P P-T cortex<br><br>note: ↓ rCBF in AD pts. than in controls in L and R P P-T region after saline dose | no **Δ** in rCBF after rx. |

Table 2b: Main findings from PET on effects of AChE inhibitors on rCBF in AD patients

| **Authors** | **Drug** | **Rx group** | **Control group** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Tune et al., 2003 | donepezil<br><br>Measures:<br><br>RBGM & AGM | 14 mild-mod. AD pts.<br><br>Scans: baseline, after week 12, and after week 24. | 12 mild-mod. AD pts.<br><br>(treated w/placebo) | No **Δ** in relative AGM (global)<br><br>No **Δ** in RBGM | ↓ between baseline and Weeks 12 and 24 in relative AGM (global) at level of the striatum and lateral ventricles<br><br>RBGM ↓ in placebo-rx group.<br><br>↓ in R parietal lobe, L temporal lobe, R frontal lobe, and L frontal lobe relative to rx group. |
| Kaasinen et al., 2002 | donepezil (6 pts.) and rivastigmine (5 pts.)<br><br>Measure: AChE activity | 11 mild-mod. AD pts.<br><br>Scans baseline and 3 mos. into rx. | 4 elderly normal controls | AChE activity ↓ in frontal cortex; in temporal cortex; and in parietal cortex<br><br>After rivastigmine, AChE activity ↓ in frontal region; and in parietal cortex.<br><br>No difference in AChE activity between regions w/in each group. | no sig **Δ** from baseline to 2nd scan in any region. |

| **Authors** | **Drug** | **Rx group** | **Control group** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| | | | | When rx groups combined, difference between frontal and temporal activity differed | |
| Shinotoh et al., 2001 | donepezil<br><br>Measure: AChE activity | 3 probable AD patients;<br><br>Scans: baseline and 1-2 mos. into rx. | 14 age-matched untreated normal controls;<br><br>Scans: baseline and 11 mos. later. | At baseline, AChE activity was reduced more than normal controls<br><br>In AD pts., AChE activity was ↓ in the cerebral cortex during rx relative to baseline. | no sig. **Δ** in AChE activity from baseline to follow-up scan. |
| Kuhl et al., 2000 | donepezil<br><br>Measure: AChE activity | 9 mild AD pts.<br><br>Scans: baseline, at 5-10 weeks and at 8-26 weeks. | 6 normal elderly controls receiving single infusion of physostigmine<br><br>scans: baseline and after infusion of drug. | after donepezil, ↓ in AChE activity from pre-rx values uniformly across cerebral cortex with larger ↓ in the striatum, thalamus, and pontocerebellar structures. | ↓ from pre-rx in AChE activity<br>across cerebral cortex, striatum, thalamus, and pontocerebellar structures. |
| Potkin et al., 2001 | Rivastigmine<br><br>Measure: BGM | 20 mild-mod. AD pts.<br><br>Scans: baseline and after 26 weeks of rx. | 7 mild-mod. AD pts. on placebo | Global ↑ in responders (15) compared non-responders (5)<br><br>Responders: ↑ in DLPFC, parahipppocampal gyrus, orbital cortex, medial thalamus, mesopontine tegmentum, amygdala, SI, pallidum, extended amygdala, and nBM. | No **Δ** in BGM |

| **Authors** | **Drug** | **Rx group** | **Control group** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| | | | | Responders: ↑ in hipp. compared to non-responders and placebo rx pts. | |
| Blin et al., 1998 | Physostigmine<br><br>Measure: BGM | 10 mild-mod. AD pts.<br><br>Scans: during placebo infusion and drug infusion | 10 age-matched normal controls<br><br>scans: during placebo infusion and drug infusion | ↓ in BGM in each ROI.<br><br>AD pts. showed bigger ↓ in BGM after rx than normal controls in every ROI. | ↓ after rx in PFC and striatum &<br>no difference in mean glucose consumption. |
| Nordberg et al., 1998 | tacrine<br><br>Measure: BGM | 3 mild AD pts.<br><br>Scans:<br>4-6 scans | None | (no p-values provided in article)<br>↓ BGM in temporal cortex and frontal cortex at baseline<br><br>after long-term rx, pts. showed ↑ BGM in frontal cortex, temporal cortex, hippocampus, and putamen. | N/A |

| **Authors** | **Drug** | **Rx group** | **Control group** | **Significant Δ in Rx group** | **Significant Δ in control group** |
|---|---|---|---|---|---|
| Blin et al., 1994 | physostigmine<br><br>Measure: RCGM | 6 mod. AD pts.<br><br>Scans: after placebo and after physostigmine | 9 age-matched normal controls<br><br>scans: after placebo and after scopolamine | no **Δ** from placebo to physostigmine infusion.<br><br>When values from thalamus, striatum, cerebellum, and limbic structures combined into one value, making 12 total region ROIs, there was ↓ from placebo to physostigmine.<br><br>Using 19 ROIs, RCGM after physostigmine was negatively correlated with RCGM after scopolamine | ↑ in RCGM from placebo to scopolamine infusion for all brain regions except thalamus. |
| Nordberg et al., 1992 | tacrine<br><br>Measure: BGM | 3 mild-mod. AD pts.<br><br>Scans: baseline, at 3 weeks, and after 3 months of rx. | None | Only 2 pts. showed ↑ in BGM at 3 months relative to baseline<br><br>2 pts. showed ↑ in temporal and frontal cortices, hipp./parahipp. and putamen/pallidum | N/A<br><br>. |

| | | | | | |
|---|---|---|---|---|---|
| Tune et al., 1991 | physostigmine<br><br>Measure: CGM | 4 probable AD pts.<br><br>Scans: baseline and after physostigmine. | none | No **Δ** in CGM | N/A |

**Table 2c: Main findings from fMRI on effects of AChE inhibitors in AD and MCI patients**

| Authors | Drug | Rx group | Control group | Task | Sig Δ in Rx group | Sig Δ in control group |
|---|---|---|---|---|---|---|
| Saykin et al., 2004 | donepezil<br><br>fMRI | 9 elderly adults with amnestic MCI<br><br>Scans: baseline during task and after 10.78 weeks during task while on drug | 9 age-matched normal controls | Both groups of subjects performed working memory (WM) task during scans | relative to controls, pts. showed ↑ activity in L SFG (BA 9), and in L occipital region.<br><br>pts. greater ↑ in activity in temporal lobe from time 1 to time 2, mostly in L. DLPFC<br><br>↑ in frontal activity in pts. correlated with improved performance on WM task. | BL activation of frontal and parietal cortex during both scans.<br><br>activation pattern changed little between both scans |
| Rombouts et al., 2002 | rivastigmine<br><br>fMRI | 7 mild AD pts.<br><br>Scans: drug-free and after single dose of drug | none | 7 pts. performed face encoding task in both scans<br><br>5 pts. did WM task during both | During face encoding, rivastigmine ↑ BL activation in fusiform gyrus.<br><br>**Δ** in 'Simple working memory' after rx showed ↑ activation in the L MFG and L SFG. | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | scans (only 4 received rivastigmine condition) | **Δ** in 'increased working memory' after rx showed ↑ in activation in the L MFG, R SFG, and R IFG. | |

Table 3: Summary of experimental hypotheses

| |
|---|
| **Neurochemical hypothesis**<br><br>▪ Functional connectivity will significantly increase after donepezil between the medial septal nuclei and the left and right hippocampus. |
| **Neuropathology hypothesis (hippocampus, DLPFC)**<br><br>▪ Functional connectivity in the ipsilateral and contralateral connections between hippocampus and DLPFC will increase. |
| **Neurocognitive: verbal fluency (hippocampus, Broca's area, DLPFC)**<br><br>▪ Functional coherence in the connections of the verbal fluency network will increase.<br><br>▪ Change in functional coherence of the connections comprising the verbal fluency network will correlate positively with change in performance on FAS |
| **Neurocognitive: episodic memory (medial septal nuclei, hippocampus, Broca's area, DLPFC)**<br><br>▪ Functional coherence in the connections of the episodic memory network will increase.<br><br>▪ Change in functional coherence of the connections comprising the episodic memory network will correlate positively with change in performance on LM I. |

Table 4: Neuropsychological test performance in patients with AD (n = 11) before and after treatment

| Variable | Pre-treatment | Post-treatment |
|---|---|---|
| | M (SD) | M (SD) |
| FAS (raw score) * | 28.09 (10.06) | 32.09 (11.64) |
| LM I (raw score) | 21.27 (8.66) | 21.09 (7.89) |

* $p < .05$

FAS=letter fluency, LM I=Logical Memory

Table 5: Means and standard errors (s.e.), pre and post, for all connections

| Name of network | Pre Means | Pre s.e. | Post Means | Post s.e. |
|---|---|---|---|---|
| **AVERAGE FIT** | | | | |
| LHIPP-LDLPFC * | .049 | .038 | -.048 | .033 |
| RHIPP-LDLPFC | -.008 | .063 | .022 | .026 |
| LHIPP-RDLPFC | .033 | .046 | .015 | .038 |
| MEDSEP-LHIPP | .009 | .148 | .044 | .102 |
| LHIPP-LBROCA | .095 | .094 | -.041 | .102 |
| RHIPP-RDLPFC | .067 | .056 | .039 | .055 |
| RHIPP-RBROCA | .104 | .057 | .007 | .192 |
| MEDSEP-RHIPP | .011 | .096 | .155 | .119 |
| LHIPP-RBROCA | .209 | .124 | -.044 | .086 |
| LBROCA-RDLPFC | .068 | .059 | .175 | .086 |
| RHIPP-LBROCA | .157 | .086 | .101 | .076 |
| RBROCA-LDLPFC | .115 | .040 | .160 | .055 |
| LBROCA-RBROCA | .330 | .095 | .084 | .114 |
| RBROCA-RDLPFC | .188 | .069 | .281 | .053 |
| LBROCA-LDLPFC- | .261 | .053 | .252 | .060 |
| LHIPP-RHIPP | .344 | .124 | .242 | .126 |
| LPVC-RPVC | .362 | .100 | .456 | .099 |
| LDLPFC-RDLPFC * | .413 | .088 | .720 | .099 |
| **SPATIAL EXTENT** | | | | |
| MEDSEP-RHIPP | .052 | .028 | .031 | .018 |
| LHIPP-RBROCA | .080 | .022 | .041 | .019 |
| RBROCA-LDLPFC | .045 | .013 | .093 | .027 |
| MEDSEP-LHIPP | .068 | .031 | .076 | .041 |
| RHIPP-LDLPFC | .083 | .028 | .077 | .030 |
| LHIPP-LDLPFC | .099 | .029 | .063 | .026 |
| LBROCA-RDLPFC | .047 | .015 | .117 | .038 |
| LBROCA -RBROCA | .071 | .027 | .094 | .050 |
| RHIPP-RBROCA | .099 | .036 | .069 | .035 |
| LHIPP-RDLPFC | .115 | .028 | .062 | .031 |
| RHIPP-RDLPFC | .108 | .035 | .070 | .028 |
| RHIPP-LBROCA | .097 | .035 | .094 | .040 |
| LBROCA-LDLPFC | .091 | .026 | .163 | .050 |
| LHIPP-LBROCA | .142 | .049 | .072 | .023 |
| RBROCA-RDLPFC | .063 | .016 | .165 | .042 |
| LDLPFC-RDLPFC | .142 | .032 | .161 | .039 |
| LHIPP-RHIPP | .222 | .059 | .126 | .045 |
| LPVC-RPVC | .254 | .084 | .360 | .117 |

* = significant change in connectivity following treatment ($p < .05$)
hipp=hippocampus, PVC=primary visual cortex, DLPFC=dorsolateral prefrontal cortex

Table 6: Pre and post means and standard errors for the three region pairs (including ipsilateral and contralateral connections).

| | Pre | | Post | |
|---|---|---|---|---|
| Name of network | Means | s.e. | Means | s.e. |
| Average Fit | | | | |
| HIPP-DLPFC | .035 | .043 | .007 | .024 |
| HIPP-BROCA | .141 | .051 | .006 | .079 |
| BROCA-DLPFC | .158 | .036 | .217 | .049 |
| Spatial Extent | | | | |
| HIPP-DLPFC | .101 | .023 | .068 | .016 |
| HIPP-BROCA | .104 | .021 | .069 | .016 |
| BROCA-DLPFC | .062 | .011 | .134 | .035 |

Table 7: Correlation coefficient (Pearson r) of connectivity change with behavior change for Average Fit and Spatial Extent for all 18 connections

| | **Average fit** | | **Spatial extent** | |
|---|---|---|---|---|
| Connection name | FAS | LM I | FAS | LM I |
| ***Verbal fluency/episodic memory connections*** | | | | |
| LHIPP-RBROCA | .162 | -.233 | .289 | -.185 |
| RHIPP-LBROCA | -.718** | .101 | .122 | -.099 |
| RHIPP-RBROCA | .091 | -.394 | .258 | -.302 |
| LHIPP-LBROCA | -.718** | -.253 | -.046 | -.406 |
| RHIPP-RDLPFC | -.166 | -.232 | .078 | -.272 |
| LHIPP-LDLPFC | -.157 | -.195 | .460 | .124 |
| RHIPP-LDLPFC | -.164 | .212 | .188 | -.029 |
| LHIPP-RDLPFC | -.367 | -.391 | .302 | .172 |
| LBROCA-LDLPFC | -.419 | .149 | .382 | .358 |
| RBROCA-RDLPFC | .183 | .220 | .071 | .775* |
| RBROCA-LDLPFC | .324 | -.079 | .211 | .600* |
| LBROCA-RDLPFC | -.142 | -.718** | .542* | .258 |
| LHIPP-RHIPP | -.182 | -.068 | .147 | .029 |
| LBROCA-RBROCA | -.123 | -.062 | .267 | .251 |
| LDLPFC-RDLPFC | .361 | -.492 | .384 | -.052 |
| ***Episodic memory connections*** | | | | |
| MEDSEP-LHIPP | -.083 | .194 | -.306 | .668* |
| MEDSEP-RHIPP | -.017 | -.147 | -.278 | -.072 |
| ***Non-behavior connection*** | | | | |
| LPVC-RPVC | .359 | -.589* | .614* | -.224 |

One-tailed parametric test: *<.05; ** <.01

FAS=letter fluency, LM I=Logical Memory

Table 8: Pre and post means and standard errors of overall connectivity defined by Spatial Extent for responders and non-responders (defined by performance on FAS and LM I, respectively)

FAS

| | Pre | | Post | |
|---|---|---|---|---|
| Responders/Non-responders | Means | s.e. | Means | s.e. |
| Responders | .100 | .017 | .134 | .024 |
| Non-responders | .110 | .018 | .076 | .026 |

LMI

| | Pre | | Post | |
|---|---|---|---|---|
| Responders/Non-responders | Means | s.e. | Means | s.e. |
| Responders | .112 | .018 | .109 | .029 |
| Non-responders | .098 | .017 | .106 | .027 |

FAS=letter fluency, LM I=Logical Memory

Table 9: Components of clusters of change in connectivity with left inferior frontal gyrus

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **cluster 1** | | | | |
| 1 | -19, 32, 30 | 6.58 | Left superior frontal gyrus (BA 9) | 9.4 % overlap with superior frontal gyrus |
| 2 | -3, 22, 21 | 5.09 | Left anterior cingulate gyrus (BA 24) | 8.8 % overlap with anterior cingulate |
| 3 | -13, 14, 13 | 7.13 | Left caudate body | 8.1 % overlap with caudate |
| **cluster 2** | | | | |
| 1 | 38, 19, -33 | 5.37 | Right superior temporal gyrus | 17.0 % overlap with superior temporal gyrus |
| **cluster 3** | | | | |
| 1 | 24, 54, 27 | 6.322 | Right superior frontal gyrus and BA 10 | 32.2 % overlap with superior frontal gyrus |
| 2 | 34, 41, 23 | 5.544 | Right middle frontal gyrus | 17.7 % overlap with middle frontal gyrus |
| **cluster 4** | | | | |
| 1 | 49, -33, 55 | 5.079 | Right inferior parietal lobule (BA 40) | 30.3 % overlap with inferior parietal lobule |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

Table 10: Components of clusters that change in connectivity with right inferior frontal gyrus

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **cluster 1** | | | | |
| 1 | 4, -29, 35 | 5.046 | Right cingulate gyrus (BA 31) | 25.9 % overlap with cingulate gyrus |
| **cluster 2** | | | | |
| 1 | -7, -52, -31 | 4.896 | Left cerebellar tonsil | 43.5 % overlap with cerebellar tonsil |

*Note.* Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

Table 11: Components of clusters that change in connectivity with left DLPFC

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | 37, -19, 14 | 5.542 | insula | 16.5 % overlap with insula |
| **Cluster 2** | | | | |
| 1 | 23, 42, 34 | 3.998 | Right superior frontal gyrus (BA 9) | 38.3 % overlap with superior frontal gyrus; |
| 2 | 5, 21, 46 | 5.868 | Right medial frontal gyrus (BA 8) | 28.3 % overlap with medial frontal gyrus, |
| **Cluster 3** | | | | |
| 1 | -54, -42, 19 | 5.212 | Left superior temporal gyrus; | 38.3 % overlap with superior temporal gyrus; |
| 2 | -52, -50, 23 | 6.12 | Left supramarginal gyrus (BA 40) | 24.4 % overlap with supramarginal gyrus |
| **Cluster 4** | | | | |
| 1 | -41, -35, 18 | 3.363 | Left insula and BA 13 | 39.6 % overlap with insula |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

DLPFC = dorsolateral prefrontal cortex

Table 12: Components of clusters that change in connectivity with right DLPFC

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | -2, 3, 56 | 6.068 | right medial frontal gyrus | 10.5 % overlap with medial frontal gyrus |
| **Cluster 2** | | | | |
| 1 | -40, -49, 39 | 5.969 | Left inferior parietal lobule and BA 40 | 29.0 % overlap with Inferior Parietal Lobule; 10.6 % overlap with supramarginal gyrus (BA 40) |
| **Cluster 3** | | | | |
| 1 | -13, -47, -36 | 4.229 | Left cerebellar tonsil | 6.9 % overlap with Cerebellar Tonsil |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

DLPFC = dorsolateral prefrontal cortex

Table 13: Components of clusters that change in connectivity with left hippocampus

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | 18, -66, 0 | 4.949 | Right lingual gyrus and BA 19 | 30.5 % overlap with Lingual Gyrus;<br>20.4 % overlap with Brodmann area 19 |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

Table 14: Components of clusters that change in connectivity with right hippocampus

| Cluster Subset | Peak coordinates | Peak t-value | Region | % of the cluster components which overlap with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | 16, -43, -34 | 4.088 | Right cerebellar tonsil | 24.1 % overlap with Culmen; 21.2 % overlap with Cerebellar tonsil |
| **Cluster 2** | | | | |
| 1 | -19, 17, -1 | 3.474 | Left leniform nucleus and left putamen | 15.4 % overlap with Lentiform Nucleus; 11.6 % overlap with Putamen |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

Table 15: Components of clusters that change in connectivity with medial septal nuclei

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | 45, 30, 19 | 3.471 | Right middle frontal gyrus and BA 46 | 36.1 % overlap with Middle Frontal Gyrus;<br>8.8 % overlap with Brodmann area 9;<br>8.0 % overlap with Brodmann area 46 |
| 2 | 49, 25, 9 | 4.696 | Right inferior frontal gyrus and BA 45 | 29.7 % overlap with inferior frontal Gyrus;<br>6.5 % overlap with Brodmann area 45 |
| **Cluster 2** | | | | |
| 1 | 51, -5, 35 | 4.638 | Right precentral gyrus and BA 6 | 28.0 % overlap with Precentral Gyrus, 27.2 % overlap with Brodmann area 6 |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior

Table 16: Components of clusters that change in connectivity with left primary visual cortex

| | Peak coordinates | Peak t-value | Region | % of the component which overlaps with the Talairach region |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | 17, -43, -19 | 5.79 | Right anterior cerebellar quadrangular hemisphere (lobule IV) (press, et al… | 28.6% overlap with culmen; 5.8% overlap with cerebellar tonsil |
| **Cluster 2** | | | | |
| 1 | -17, -86, 8 | 5.49 | Left cuneus and BA 17 | 54.1% overlap with lingual gyrus; 32.2% overlap with cuneus |
| **Cluster 3** | | | | |
| 1 | -33, -44, -12 | 3.58 | Left fusiform gyrus | 9.6% overlap with fusiform gyrus |

Talairach coordinates are shown in parentheses (x, y, z: -x = left, -y = posterior, -z = inferior)

# FIGURES

Left DLPFC seed

Right DLPFC seed

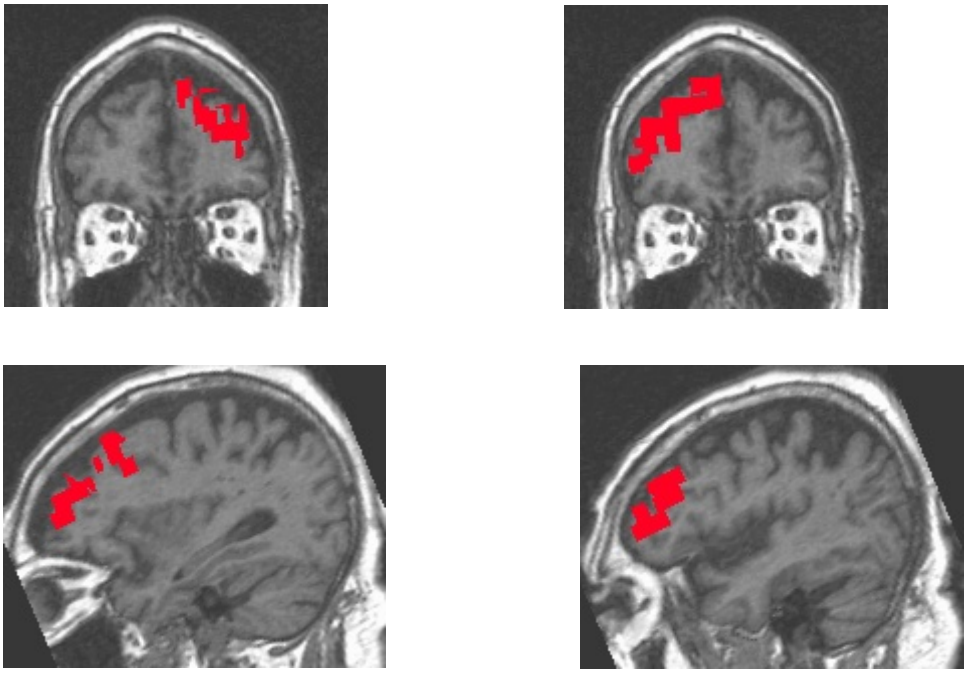


Figure 1a

Left IFG seed

Right IFG seed

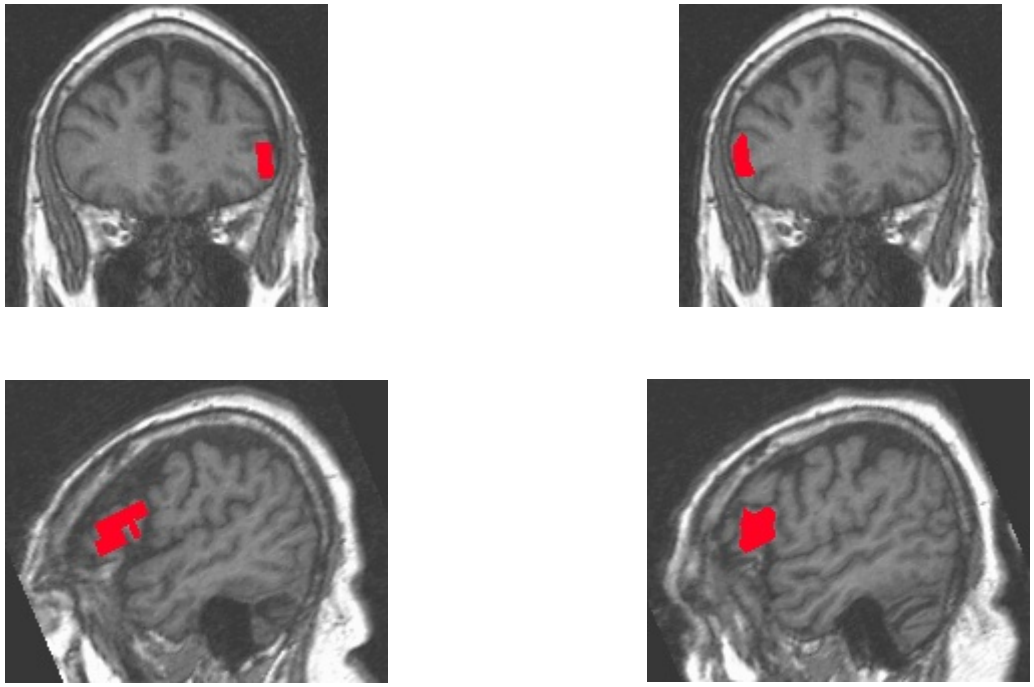
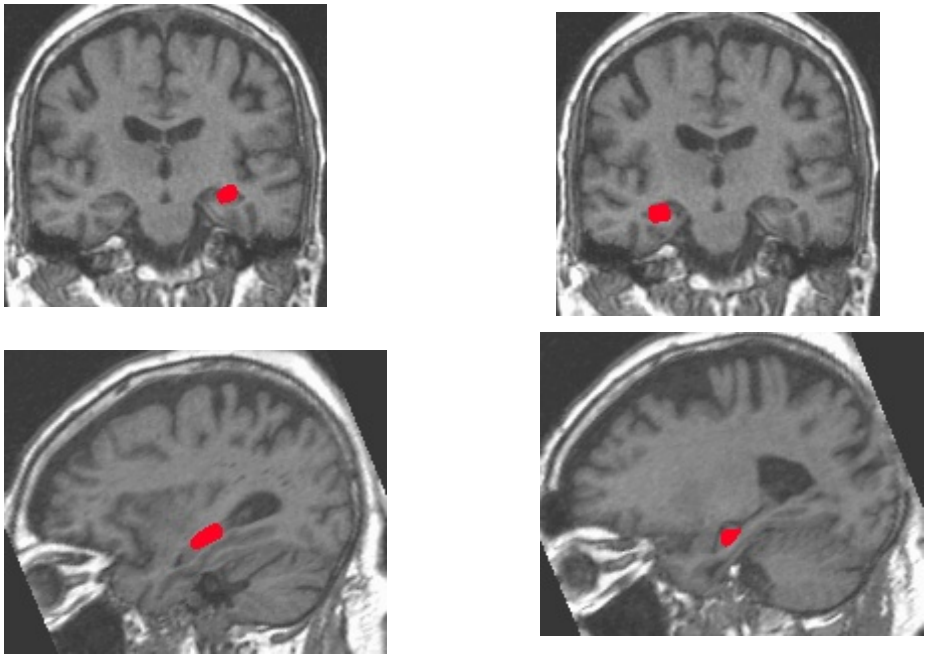


Figure 1b

Left hippocampus seed

Right hippocampus seed



1c

Left PVC seed

Medial septal nuclei seed

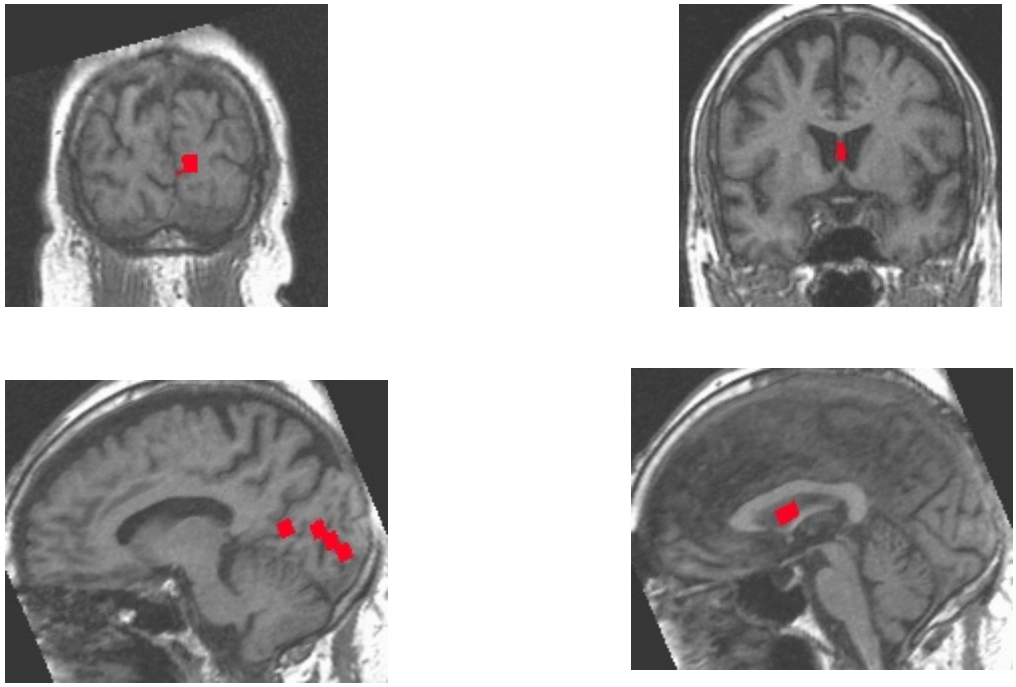


Figure 1d

Figure 1 (a-d): eight seed masks overlaid on an individual subject's high resolution image: left and right DLPFC; left and right IFG, left and right hippocampus; left PVC; and medial septal nuclei

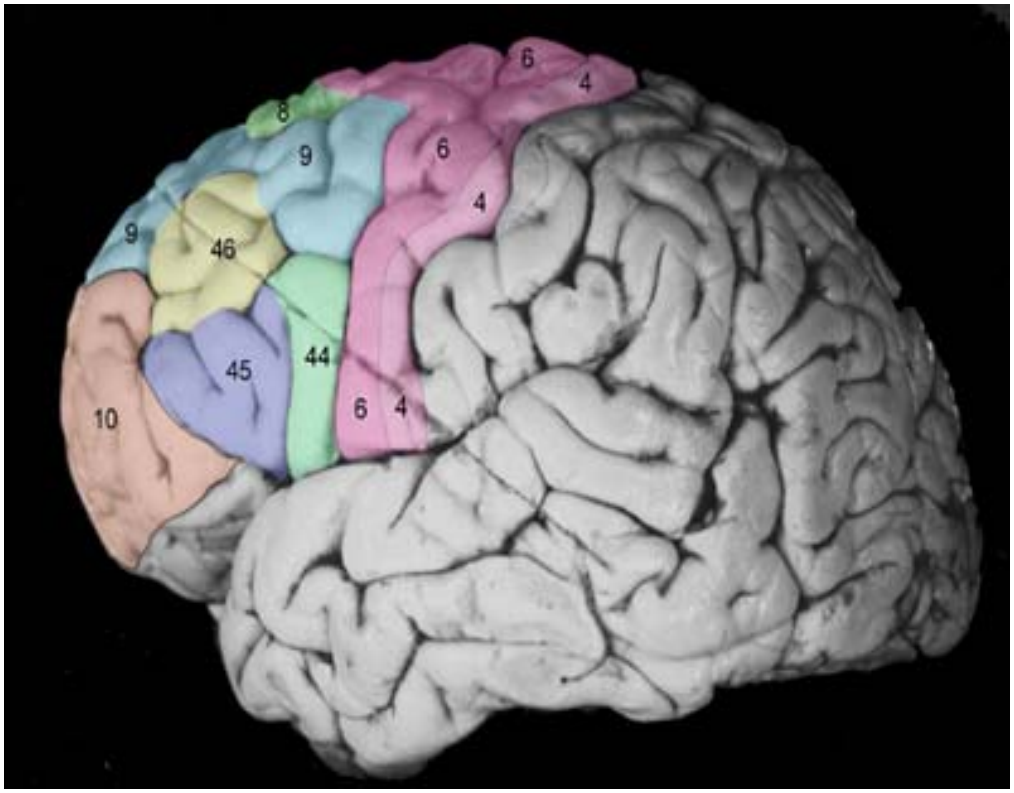



Figure 2a: lateral sagittal surface view

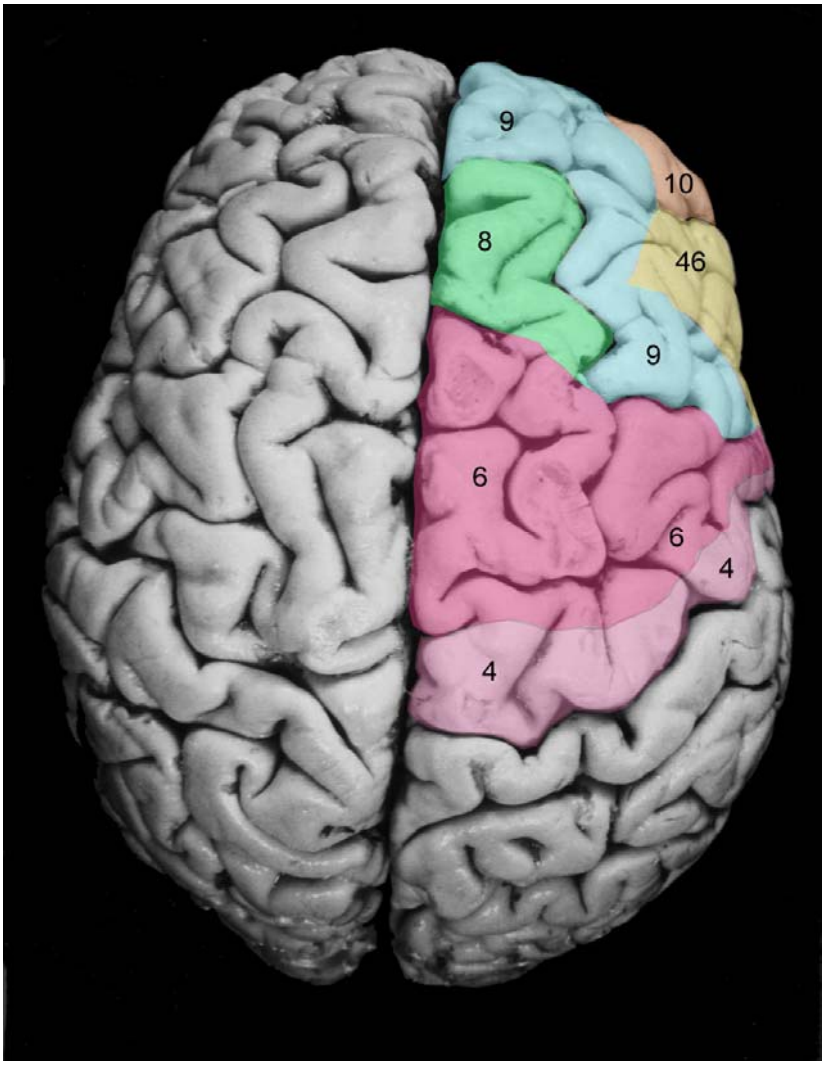



Figure 2b: axial surface view

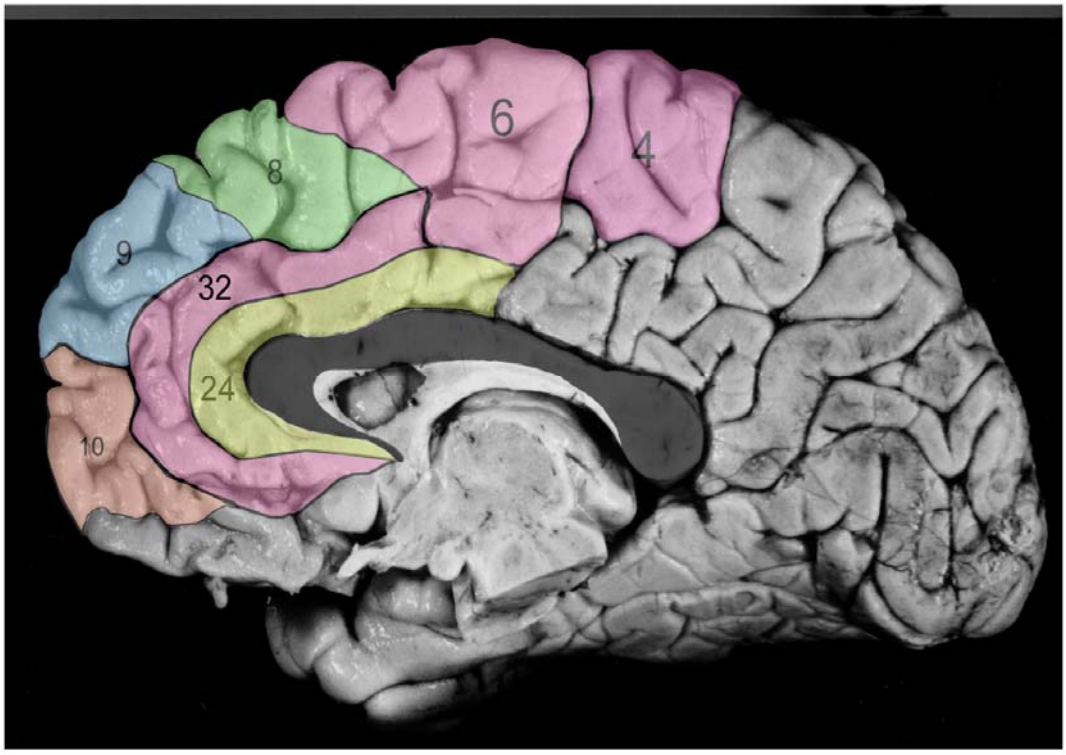



Figure 2c: Medial view

Figure 2(a-c): Brodmann Areas probability map showing views of the sagittal lateral, sagittal medial, and axial surface of the brain (Aboitiz, F. et al.)

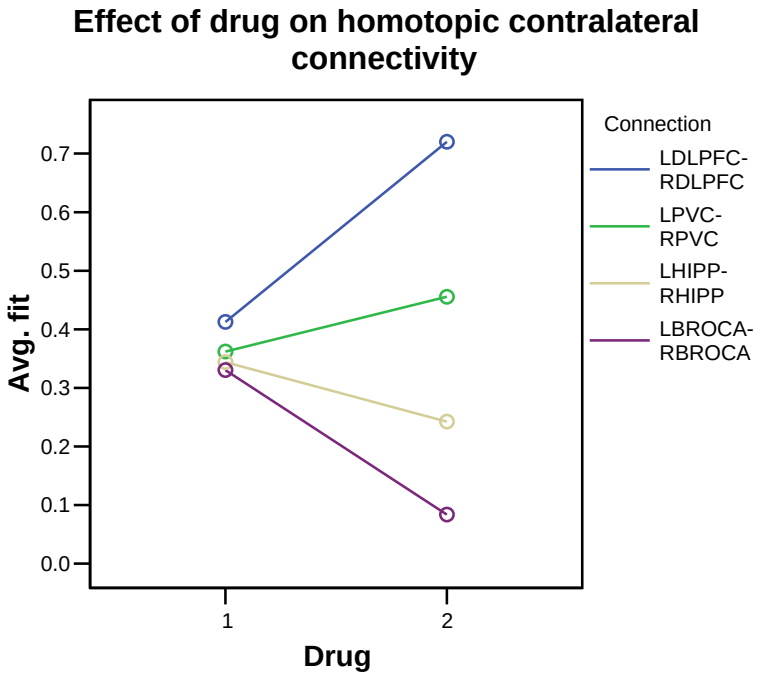



Figure 3. Effect of drug on homotopic contralateral connectivity

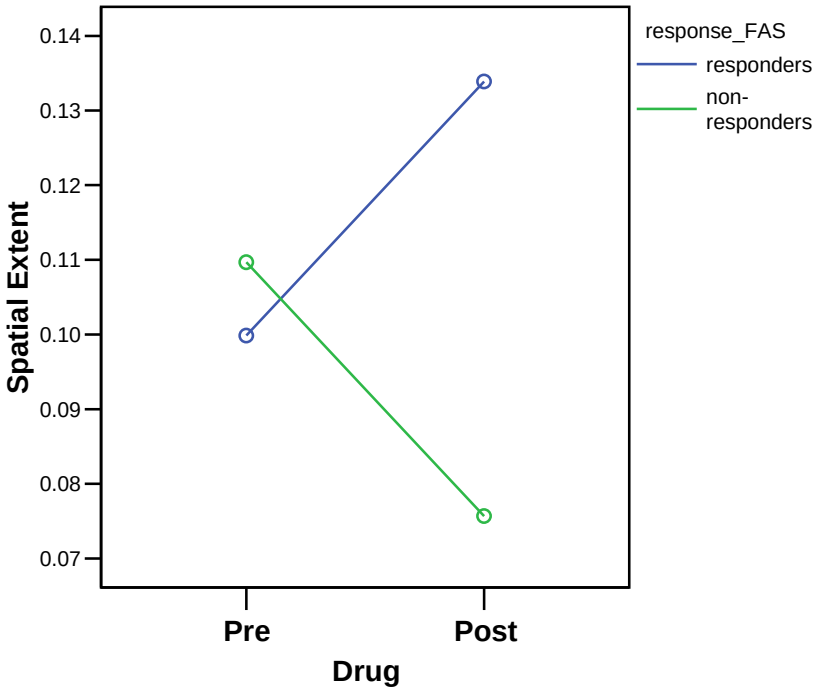



Figure 4. Effect of the drug on overall connectivity (Spatial Extent) in responders and non-responders (defined by FAS)

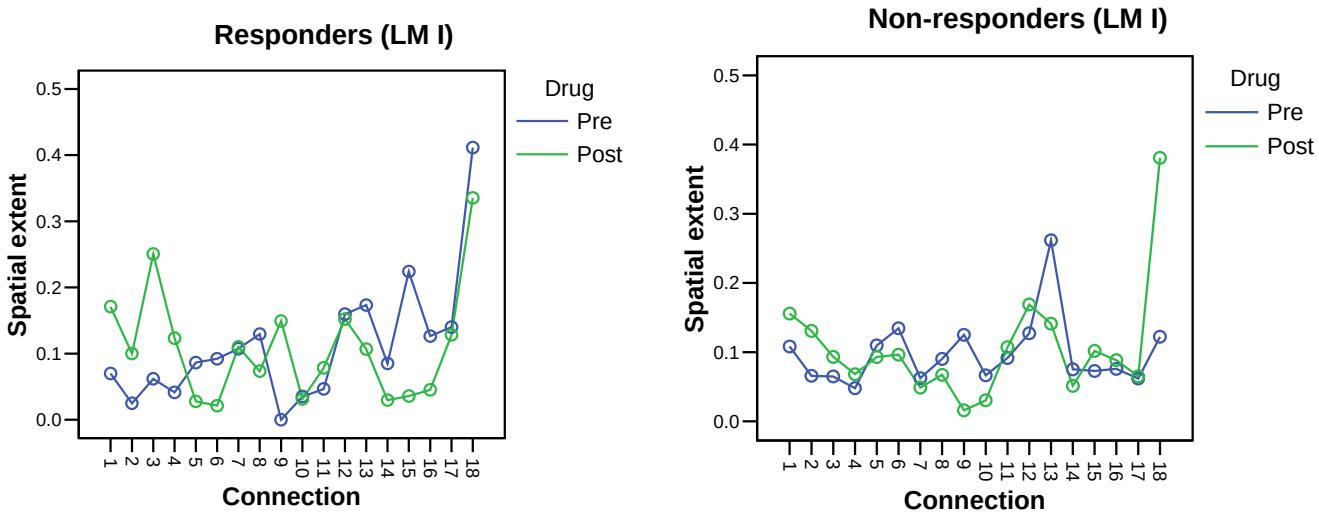
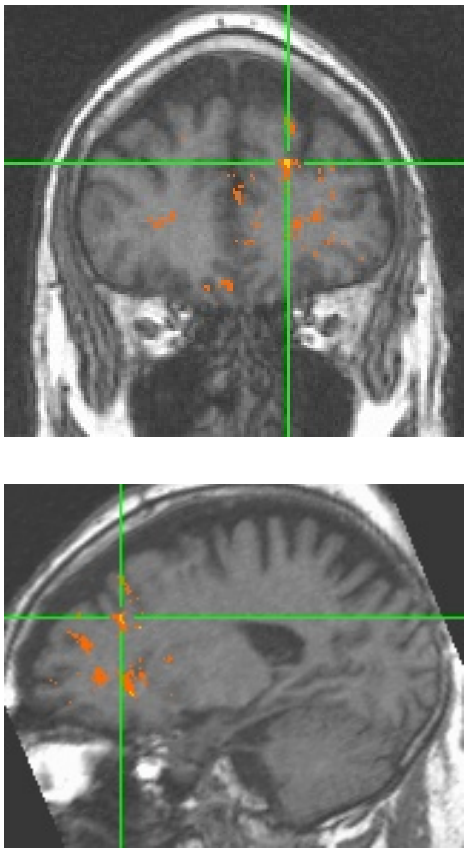



Figure 5. Interaction of Connection (SE) * Drug (pre, post) * Response (LM I) (responders, non-responders

Connectivity change with left IFG cluster 1
Left Superior frontal gyrus (BA 9)
(-19, 32, 30)



Connectivity change with left IFG cluster 1
Right middle frontal gyrus
(34, 41, 23)

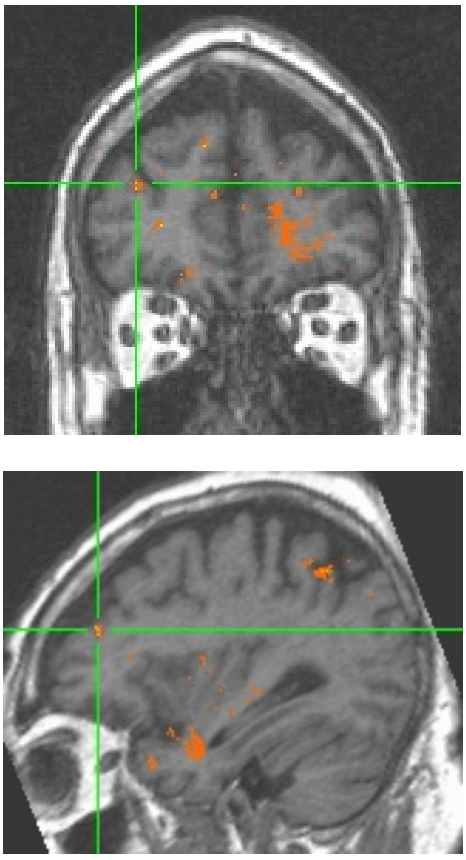


Figure 6a

Connectivity change with left DLPFC cluster 1
Right superior frontal gyrus
(23, 42, 34)

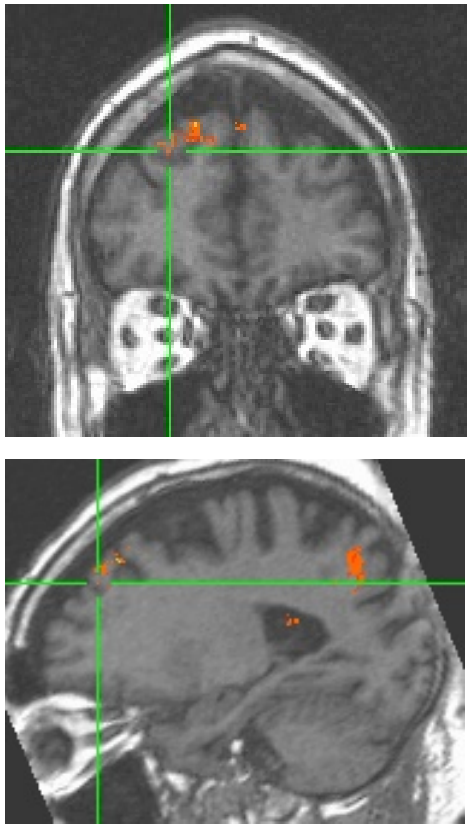


Figure 6b

Connectivity with medial septal nuclei cluster 1
Right middle frontal gyrus (BA 46)
(45, 30, 19)

Connectivity with medial septal nuclei cluster 1
Right inferior frontal gyrus and BA 45
(49, 25, 9)

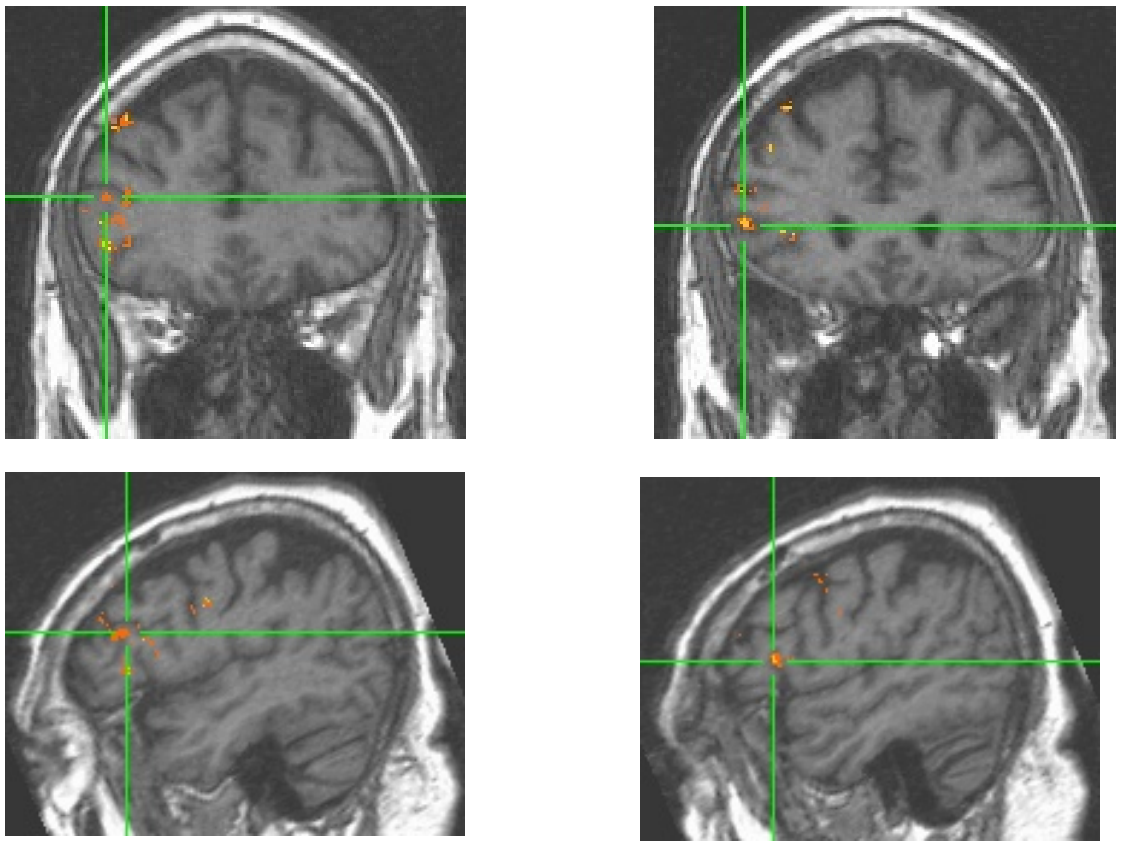
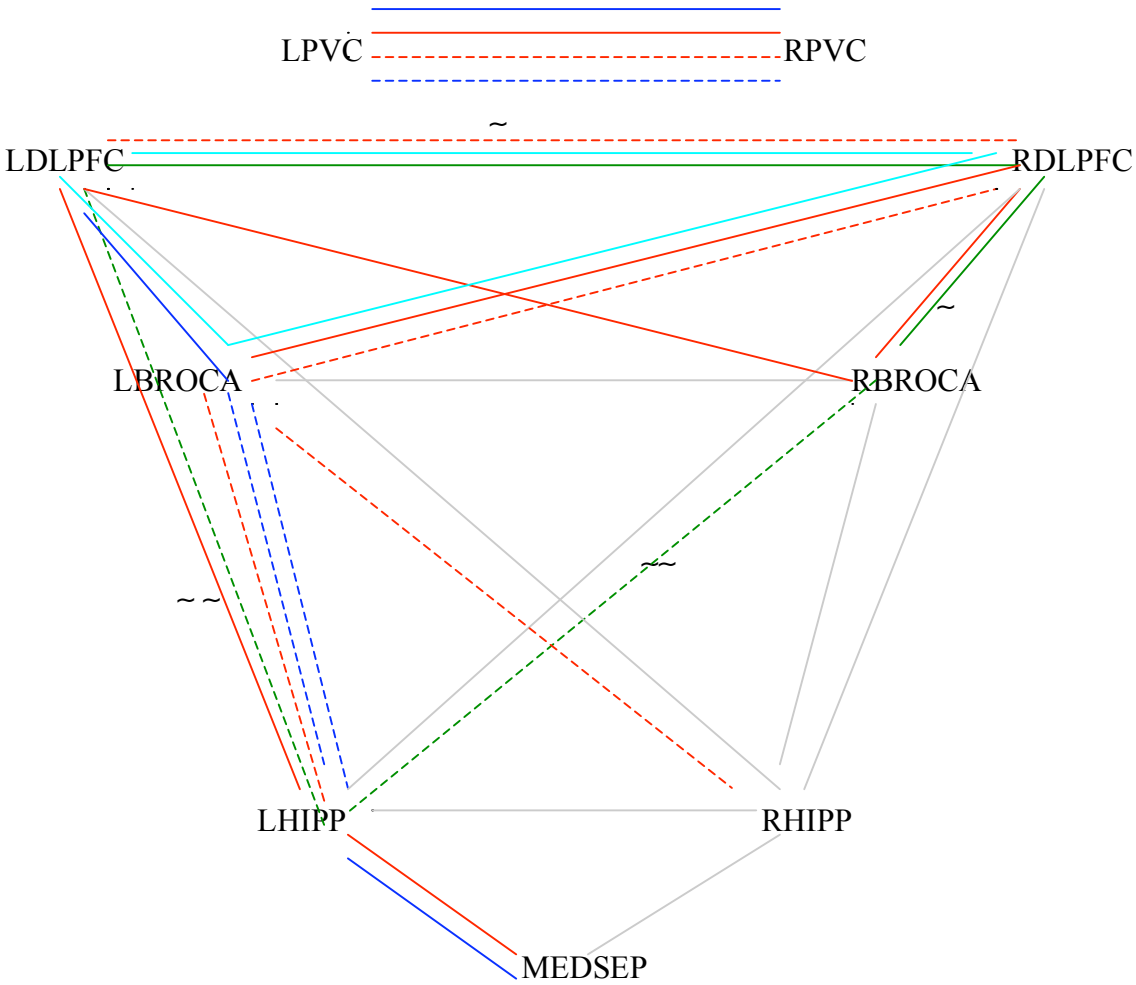


Figure 6c

Figure 6(a-c): Maps show clusters of significant change in functional coherence with areas that were target ROIs in this study, shown in both the coronal and sagittal views. Group data are overlaid on an SPGR volume from a single representative subject in Talairach coordinate space. Talairach coordinates in parentheses refer to the location of cross hairs.




Red= Correlation of connectivity with behavior +————

Blue= Interaction of Response x Drug - ----------

Green= Main effect of Drug ~ .07 > p > .05

Turquoise= Exploratory analyses ~~ .09 > p > .07

Figure 7: A schematic diagram depicting all connections showing a significant drug effect, significant correlations of connectivity change with behavior change, and significant Connection * Response interactions.

# APPENDIX

## DEFINITIONS OF REGIONS OF INTEREST

Inferior frontal gyrus (pars opercularis (BA 44) and pars triangularis (BA45)

The following texts and resources aided in defining the IFG corresponding to BA 44 (pars opercularis) and BA 45 (pars triangularis): Foundas et al. (2001), Weisberg, Browning, & Weinberger (2001); Protocol for tracing the inferior frontal cortex (Laboratory of neuroimaging, LONI, website UCLA); Duvernoy et al. (1999); Amunts et al. (1999); Ono, Kubik, & Abernathey (1990); 3 surface views (sagittal, axial, and coronal) of a 3-dimensional human brain surface with Brodmann's areas adapted to fit it (See Figure 2a-c) (Aboitiz, F., personal communication, Oct.1, 2005).

The inferior frontal gyrus consists of three subregions, pars opercularis, pars triangularis, and pars orbitalis. All planes were used to trace this region. The following landmarks were used to assist with definition of this ROI: the anterior horizontal ramus of pars triangularis was used as the anterior border; the precentral sulcus was used as the posterior border; the inferior frontal sulcus was used as the superior border; and the Sylvian fissure was used as the inferior border. Often, the precentral sulcus was interrupted or not continuous. In these cases, in the sagittal view, a diagonal line was drawn (following the trajectory of the sulcus) connecting the lowest identifiable point of the precentral sulcus with the Sylvian fissure as described in the protocol for tracing the inferior frontal cortex (Laboratory of neuroimaging, LONI, website UCLA website). Similarly, the inferior frontal sulcus was often interrupted. In these cases, in the sagittal plane, the shortest line linking the endpoints of the interrupted sulcus was drawn. Tracing began by identifying the location of

the pars triangularis in the sagittal plane as described by Foundas et al. (2001). In the sagittal plane, pars triangularis often looks like an upside-down triangle (Foundas et al., 2001). The different configurations of this structure are discussed by Foundas et al. (2001). When moving through the slices in the sagittal plane from medial to lateral (starting at the gyrus brevis of the insula), the ascending horizontal ramus and the anterior ascending ramus come into view. As described by Foundas et al. (2001) and seen in Ono et al.'s atlas of the cerebral sulci (1990) and Duvernoy's cerebral atlas (1999), the configuration of the two rami and the structure they bound (pars triangularis) may resemble an "I", "J", "V" or "Y" on the lateral surface in the sagittal plane. Once the pars triangularis structure was identified, the inferior frontal sulcus and Sylvian fissure became visible. The anterior border of the ROI, the anterior horizontal ramus, was followed from its origin in the Sylvian fissure to its junction with the inferior frontal sulcus, the superior border of the ROI. Next, the inferior frontal sulcus was followed caudally until its junction with the precentral sulcus was reached. When the junction of the inferior frontal sulcus and the precentral sulcus was reached, the precentral sulcus (now separating BA 44 from BA 6) was followed down until it terminated in the Sylvian fissure. In order to maximize gray matter and minimize white matter inclusion, a fixed depth from the surface (approximately 2 mm) was chosen. This depth was best kept constant in the coronal plane, since this was the plane with the best resolution and it best showed the depth of relevant sulci. The tracing along the bank of any given sulcus continued until the fundus (valley) of the sulcus was reached in the coronal plane.

Dorsolateral prefrontal cortex (DLPFC)

The following texts and resources aided in defining the DLPFC corresponding to BA 46, 46/9, 9: Petrides & Pandya (2002); Duvernoy et al. (1999); Foundas et al. (2001); in the protocol for tracing the inferior frontal cortex (Laboratory of neuroimaging, LONI, website UCLA website); Anterior cingulate gyrus Manual Tracing Protocol (NeuroImage Analysis Lab, University of North Carolina, 2005); Ono et al., 1990; and 3 lateral views (sagittal, axial, coronal) of a 3-dimensional real human brain surface with Brodmann's areas adapted to fit it (Aboitiz, F., personal communication, Oct.1, 2005).

All planes were used to trace this region. The following general guidelines were used to assist with definition of this ROI:

Inferior border part 1: The inferior frontal sulcus was used as the inferior border of the ROI separating BA 46 + BA 9 from BA 44 + BA 45.

Anterior border part 1: A vertical line originating from the junction of the inferior frontal sulcus and the anterior horizontal ramus of the pars triangularis was drawn. This line was drawn going dorsally and was used as the separating line between BA 10 and BA 46 + BA 45 (the anterior border of this portion of the ROI). This vertical line stopped at an imaginary horizontal line parallel with the anterior commissure-posterior commissure line (AC-PC line), and 2 mm below the apex of the corpus callosum, consistent with the border between BA 9 and BA 10 visualized on the medial surface view of the model brain provided by Aboitiz, F., (personal communication, Oct. 1, 2005).

Inferior border part 2 Once this imaginary line was reached, a line was drawn in the rostral direction along it (along the dorsal convexity of the lateral surface) until it reached the most rostral edge of the anterior cingulate gyrus on the medial surface.

Inferior border part 3 + anterior border part 2 Once the anterior cingulate gyrus was reached, the cingulate sulcus was followed in the dorso-posterior direction until the vertical line separating BA 46 and BA 10 was reached. Due to the fact that in some subjects the cingulate gyrus is bounded by the cingulate sulcus, and in other subjects, it is bounded by the paracingulate sulcus, it was necessary to to differentiate the two. This ensured that the cingulate gyrus was not included in the ROI.

Posterior border part 1 Starting at the junction between the inferior frontal sulcus and the precentral sulcus, the precentral sulcus was followed dorsally until the superior frontal sulcus was reached. The line just defined separated BA 44 + BA 9 from BA 6.

Superior border (part 1) Starting at the junction of the precentral sulcus and the superior frontal sulcus, the superior frontal sulcus was followed rostrally until a vertical line separating BA 46 and BA 10 was reached. This BA 46/ BA 10 separation line was a continuation of the one defined earlier as 'anterior border part 1'.

Posterior border part 2 Starting at the junction of the superior frontal sulcus and the continuation of the BA 46/ BA 10 separation line, a line was drawn dorsally following the BA 46/ BA 10 separation line until the interhemispheric fissure was reached. This line separated BA 9 from BA 8. Then, to complete the posterior

border of this ROI, this line was followed down (in the inferior direction) along the medial surface of the hemisphere until the dorso-posterior line, 'inferior border part 3 + anterior border part 2', was reached.

In order to define this region as accurately as possible using macroscopic morphological boundaries, it was necessary to continually refer to the 3-dimensional lateral surface model of a real brain (3 views of a brain surface with Brodmann's areas represented), and Duvernoy's cerebral atlas (1999 ) and Ono et al.'s atlas of Cerebral sulci (Ono, 1990).

Medial septal nuclei

The following texts aided in localizing and defining the medial septal nuclei: Duvernoy et al., 1999; Mai et al., 2004; and Defrance, 1976. The coronal plane was used to trace this region. The following general guidelines were used to assist with definition of this ROI:

As shown in the cerebral microatlas in Mai et al., 2004, in the coronal plane, as one is paging in the coronal direction from anterior to posterior direction, the medial septal nuclei extend from the first slice where the anterior commissure can be seen 8 mm caudally. In the axial plane, it extends for 7 mm at the longest point, and in the sagittal plane, it extends for 6 mm. There are separate medial septal nuclei for the left and right side. They are ventral to and abut the corpus callosum, medial to the lateral ventricles, and dorsal to the anterior commissure. Adjacent structures include the fornix, which lies inferior to the medial septal nuclei and the lateral septal nuclei, which are lateral to the medial septal nuclei

Primary visual cortex (PVC)

The following texts and resources aided in defining the PVC corresponding to BA 17: Amunts et al., 2000; Duvernoy, 1999; (Mega et al., 2002, LONI website, UCLA); Rademacher et al., 1992; Rademacher et al., 1993; and Ono, 1990.

The PVC is located along the banks of the portion of the calcarine sulcus that extends in a caudo-inferior direction from the junction of the calcarine sulcus and the parietooccipital sulcus (cuneal point) to the occipital pole. The calcarine sulcus was used as a reference landmark for tracing the PVC (Mega et al., 2002; Protocol for tracing sulcul lines, LONI website, UCLA; Rademacher et al., 1992; and Rademacher et al., 1993). In the sagittal plane, gray matter was included that extended approximately ½ cm superior and ½ cm inferior to the calcarine sulcus (Engel, S., 2004; personal communication, Oct. 1, 2005); Rademacher et al. (1992). Tracing of this region was done on the medial surface of each hemisphere (Rademacher et al., 1992) and extended laterally approximately 2 mm left or 2mm right depending on the hemisphere traced. All planes were used to trace this ROI. The following general guidelines were used to assist with definition:

Inferior border The collateral sulcus, which extends in the caudo-inferior direction and is approximately parallel to the calcarine sulcus, served as the inferior border. The collateral sulcus lies in the lingual gyrus.

Superior border The superior border was the cuneal sulcus, which extends in the caudo-inferior direction and is superior to the calcarine sulcus. The cuneal sulcus lies in the cuneal gyrus.

Anterior border The parietooccipital sulcus served as the anterior border of the ROI.

Posterior border occipital pole.

Hippocampus

The following texts and resources aided in defining the hippocampal formation corresponding to: Duvernoy et al. (2005); Duvernoy et al. (1999); and Cook, Fish, Shorvon, Straughan, & Stevens, (1992) .

The hippocampal formation is located in the medial temporal lobe. The longest extent of the hippocampal formation is in the rostral-caudal direction and is best seen in the sagittal plane. Structures that border the hippocampus dorsally are the subsplenial gyrus at the tail, the thalamus along the body, and the amygdala at the head of the structure. The hippocampal formation winds back and forth medially and laterally as it extends in the rostral-caudal direction. The hippocampal formation is bounded superiorly, medially, and laterally by cerebrospinal fluid (CSF) in the choroid fissure and the ambient cistern. It is bounded inferiorly by the white matter separating it from the parahippocampal gyrus. All planes were used to trace this ROI, with most tracing done in the coronal plane because it had the best resolution. Sagittal and axial planes were used as references.

Tracing began at the tail of the hippocampal formation and proceeded rostrally in the coronal plane. The caudal-most extent of the tail of the hippocampus is located where the end of the fornix column is at its greatest length, where it abuts the structure. In this slice, the subsplenial gyrus should be visible immediately superior to the hippocampal formation. The parahippocampal gyrus should be visible immediately inferior to it (Cook et al., 1992). Moving anteriorly, the thalamus separates the hippocampal formation from the fornix, and replaces the subsplenial cortex as the structure immediately superior to it. The alveus, a thin

lining of white matter, borders the hippocampal formation dorsally and separates it from the hippocampal fissure.

A few slices before the head of the hippocampus comes into view, the choroid plexus becomes visible and is superior to the alveus. Moving closer to the head of the hippocampus, the uncal gyrus replaces the choroid plexus as the structure immediately superior to the alveus. As you page rostrally in the coronal plane, the uncal gyrus thickens and blends in with the amygdala. Paging through the coronal slices rostrally, as the head of the hippocampus comes more into view, the amygdala becomes bigger. While tracing the hippocampal head, the alveus continued to be the critical structure that effectively differentiated the hippocampus from the amygdala.

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Liam Zaidel was born in Pasadena, California, on July 27, 1973, the son of Dahlia Zaidel and Eran Zaidel. After graduating from William H. Taft high school, Woodland Hills, California, he entered the University of California at Santa Cruz, Santa Cruz, California. He received his Bachelor of Arts degree with a major in Psychology from the University of California at Santa Cruz in June 1996. For the next four years, he worked as a research assistant in The Alzheimer's Disease Research Center at the University of California at Los Angeles (UCLA) and at the Brentwood Veterans Administration Hospital in Westwood, California. In August of 2000 he entered the Graduate School of Biomedical Sciences at the University of Texas Southwestern Medical Center at Dallas. He was awarded the degree of Doctor of Philosophy in April of 2006.

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