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An Issue Devoted To Neuroimaging

President's Message

A presidential column affords a "bully pulpit" to one lucky person. It presents a non-peer-reviewed opportunity for a single individual to advocate his agenda for an organization. In fact, the only question that I have been asked that relates specifically to my year as D40's president has been, "What's your agenda?' Surprisingly, this question came up after I assumed office. A possibly greater surprise is that I don't see myself as having "an agenda." I am not so naïve as to think that, in the course of one year, I either could, or should, set out to achieve any single substantive and heretofore unannounced goal. I hope to serve the division by advancing our profession's overall "health" through responsible leadership, and I am honored to have the opportunity to do this.

After thinking about how a profession's leadership influences its "health," there is something that I would like to suggest. However, a bit of a preamble is needed before I offer my simple idea.

My concern derives from a question: "What is the single, most important reason that I (you) chose to be a Clinical Neuropsychologist?" In other words, why are we here? Take a moment and answer this for yourself.

If your answer does not have "service to patients" at its heart, I'm worried. Here's why. I have been involved with neuropsychology for over 30 years. During this time I have listened to what many, many neuropsychologists, both the professionally "young" and "old," say about our profession and I have also observed what they do. I've concluded that the vast majority of us do what we do because we are truly interested in helping others. This is almost universally true for our newest colleagues. But as each generation of neuropsychologists matures a small number of us lose focus and appear to place personal ambitions and reputations above service to patients. For many, this is a benign "shift" because they continue serving patients adequately, if not well. However, it can be a malignant change of focus when the affected person gains sufficient professional stature, maybe even becoming "a name," that allows her to rise to leadership positions. So, what's the problem?

Unless all neuropsychologists remain focused on the people we serve, our profession is less than it can, and should, be. When any of us is more concerned with personal/professional reputations and

In This Issue

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From The Editor

I am very pleased to be serving as editor of Newsletter 40 and excited to be beginning my term as editor with this very timely issue dedicated to Neuroimaging. As many of you know, neuroimaging has revolutionized the field of neuropsychology. This issue contains very exciting articles on neuroimaging in populations such as pediatrics, psychiatry, rehabilitation, and neurology. I would like to offer my sincere thanks to all who have taken the time to contribute to this issue. We hope you enjoy this issue of Newsletter 40 and look forward to seeing you at INS!

Nancy D. Chiaravalloti, PhD
Editor

Mapping Brain Structure in First Episode Schizophrenia

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Neuropsychology has been revolutionized already by neuroimaging and this revolution is still very much in progress. Considerable attention is paid to the development of functional imaging techniques, particularly functional MRI, which is yielding great insights into the engagement of distributed neural systems during cognitive tasks. It can be argued that fMRI has turned the major paradigm for neuropsychology research on its head (perhaps in the right direction?) by looking at the "brain as the dependent variable." This stands in contrast to the traditional paradigms focused on studying functional impairments associated with specific brain deficits such as those associated with a particularly diagnostic syndrome or focal lesion. Perhaps less widely appreciated are breakthroughs in mapping of brain *structure*. It is possible that these breakthroughs may have a role similar to that played by functional imaging in reversing the classic paradigm of neuropsychology. Older studies focused on finding deficits associated with abnormalities in specific locations of the brain as observed on scans. The new methods parallel functional imaging in their capacity to map individual differences on diverse measures — including diagnostic group effects, scores on neuropsychological tests, and heritability estimates from genetic studies — directly onto the variation in brain structures.

We have been fortunate to apply these techniques in our studies of people with schizophrenia. In a bicoastal collaborative effort we have already mapped multiple brain structure differences between patients and healthy people. At the Zucker Hillside Hospital Division of North-Shore Long Island Jewish Health System (NSLIJ), we collected high resolution T1-weighted MRI scans of the brain in large samples of people who were experiencing their first episode of schizophrenia, along with healthy volunteers matched to the patients on key demographic characteristics. In addition to the MRI scans, these patients received extensive clinical and neuropsychological characterization starting during the first episode of illness, and then continuing through various phases of prospective longitudinal follow-up. Some measurements of brain structure were conducted at NSLIJ, but we then worked in the Laboratory of Neuro Imaging (LONI) at UCLA to conduct additional detailed morphological analysis. More specifically, we took the original images, and following editing and demarcation of multiple cortical sulci, fissures, and other surface landmarks and contours, we were able to create detailed anatomical maps of the entire cortical surface, and the surface of the entire hippocampal formation. These methods can be distinguished from those sometimes used for "voxel-wise brain morphometry" (VBM) in that the usual VBM approach may not assure the correspondence of homologous points across brains; if there are errors in these homologies, differences in brain shape between individuals may be confounded with changes in the volume or density of underlying tissues. Using the LONI approach, pioneered by Paul Thompson and colleagues, which involves high dimensional warping of the brain surface to help assure the matching of homologous regions, stronger inferences can be made about the meaning and statistical significance of deformations that exist between individuals or groups of individuals.

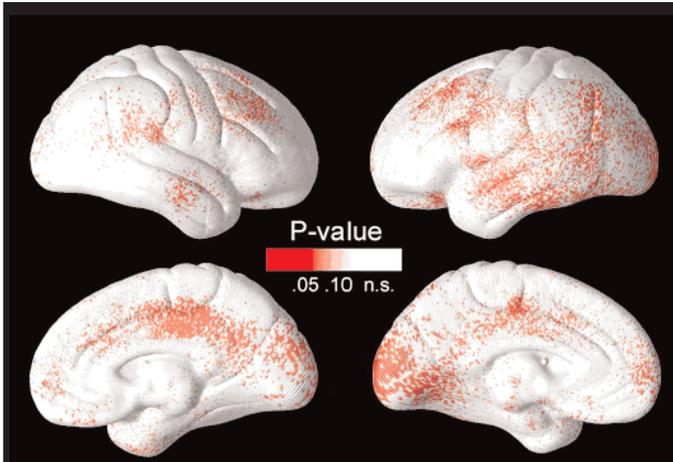Some examples of this work are presented in Figures 1 and 2.

Figure 1. Maps of cortical gray matter thickness deficits in individuals with schizophrenia (n = 72) compared to healthy volunteers (n = 78). Note the widespread pattern of gray matter thinning throughout both anterior and posterior association cortices, with greater prominence of left temporoparietal deficits on the lateral surface, and extensive deficits in cingulate gyrus on the medial surfaces.
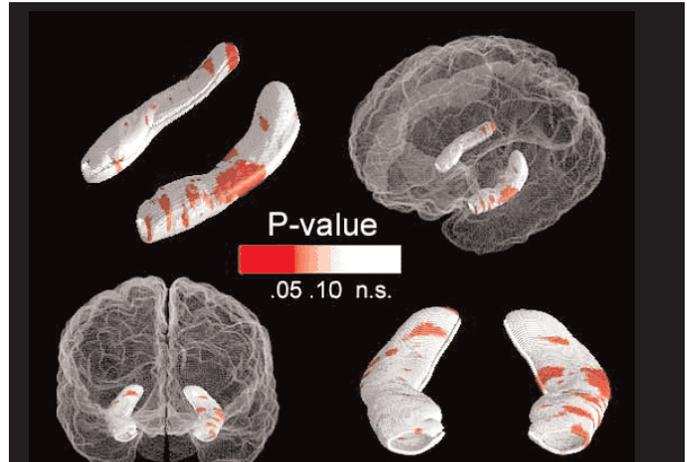

Figure 2. Statistical mapping of deformations in the hippocampal formation that distinguish individuals with schizophrenia (n = 62) from healthy volunteers (n = 60). Note that the deformations (corresponding to volume reductions) in patients are most prominent in the mid-to-anterior hippocampus and appear greater in the left hemisphere.

Figure 1 illustrates the thinning of the cortical gray matter in schizophrenia relative to healthy volunteers. The mapping of actual cortical thickness was enabled by computing the distance from the gray-white boundary to the gray-CSF boundary at 65,536 points over the cortex. The statistical significance of these results was then assessed using principal components analysis to reduce the number of variables (in this case we obtained 4 principal components together accounting for ~50% of variance, while subsequent factors explained less than 4% of variance), and then these first 4 principal component scores were used in general linear models to examine effects of diagnostic group with hemisphere as a repeated measures and with sex and age as covariates. After correcting for total brain volume, effects of diagnosis (F(1,144)=14.06, p<.0002); and age, F(1,144)=42.54, p<.00001) the model remained significant. Given the significance of these omnibus tests, we then plotted the individual significance values (uncorrected) at each cortical surface point (see Figure 1). Further details are published (Narr et al., 2004a).

Figure 2 illustrates the deformations in the hippocampal surface associated with the schizophrenia diagnosis relative to healthy volunteers. We first determined that there were significant volume reductions in the hippocampal

formation bilaterally in patients, and that these amounted to decreases of 4% to 6%. Next, we measured local deformations across the entire hippocampal surface by constructing a medial curve running along the entire antero-posterior length of each hippocampus, and then computing the radial distance from this medial curve to each surface point on the skeletonized hippocampal surface. Statistical analysis of these distance measures was then used to detect local deformations over the entire hippocampal surface. Given that analysis of these distance measures used thousands of individual t-tests, we used permutation testing, with the assignment of diagnosis randomized 100,000 times, to determine the empirical false positive rate and correct the number of significant results in the final maps of significance (see Figure 2). The regions where these deformations are most conspicuous (on the mid-to-anterior lateral hippocampal surface) correspond roughly to hippocampal fields CA1 and CA2. Further details of these findings are published (Narr et al., 2004b). These results are further interesting in light of prior reports from our studies, using conventional morphometric approaches, that reported associations of volume reductions specifically in the anterior hippocampal formation with neuropsychological deficits in executive and

Neuroimaging in Neuropsychology

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It has been over 40 years since the first concerns resonated within the field of neuropsychology that neuroimaging would effectively eliminate any important clinical or scientific contributions offered by neuropsychologists. Since that time, the medical disciplines of nuclear medicine and radiologic physics, among others, have continued to make advancements in neuroimaging including methods that provide invaluable information about the structural, electrophysiological, neurometabolic, and functional status of the brain. Interestingly, the development of neuroimaging methods that integrate information about both structural and functional brain organization has actually operated to *emphasize* the role of the neuropsychologist. The primary reason for this trend is that, because information about brain status achieved through these various techniques is often difficult to interpret without a behavioral reference point, the critical dependent variable is human behavior. The psychologist is ideally trained for the cognitive, motor, and sensory paradigm development used during brain imaging as well as the out-of-the-scanner interview and assessment that links information about the cerebral substrate to human behavior. Because of this, the psychologist has become an important figure within many multidisciplinary teams using neuroimaging techniques to better understand the effect of pathophysiology on human behavior. Moreover, while many of the novel techniques discussed herein are only beginning to be used clinically, to date, psychologists have played an important role in the application and validation of these techniques in neurologically impaired samples. The following represents a brief overview of some of the structural and functional neuroimaging techniques currently in use both for research and clinical purposes.

Functional Imaging: fMRI, PET, MEG, NIRS
Functional MRI

Blood oxygen level dependent (BOLD) MRI has become synonymous with fMRI and, largely because of its accessibility, it has grown to be the most widely used functional neuroimaging technique in the examination of behavior in humans. Put simply, fMRI is the measurement of blood flow in response to neural firing. The fMRI signal is based primarily upon the ratio of oxyhemoglobin to deoxyhemoglobin expressed as a hemodynamic response function (hrf) and this signal is influenced by multiple factors including blood flow, blood volume, and vessel size. fMRI provides excellent spatial resolution (roughly 4x4x4 mm) and good temporal resolution (about 2000 msecs). It is important to emphasize that fMRI measures neither oxygen perfusion nor neural firing, but the hrf that it does measure is reliable and well characterized.

More recently, through the use of a technique called arterial spin labeling (ASL), investigators now have developed a direct measure of oxygen perfusion by "tagging" or labeling protons by influencing their spin at the level of the internal carotid. After a short period of time, these temporarily altered protons are then examined upon reaching the cortex. This technique, pioneered over the past decade, is completely noninvasive and has begun to be applied to clinical samples in the study of motor functioning and cognition. ASL provides measures of baseline cerebral blood flow (CBF) as well as blood flow during experimental challenge which is a significant advantage because of the tight coupling between neuronal firing and CBF. Importantly, ASL is now becoming methodologically comparable to BOLD which should increase its application. For example, advancements in ASL methodology have decreased acquisition times, improved signal to noise ratio, and made whole brain coverage possible in time periods more easily tolerated by neurologic and psychiatric samples. With continued development, ASL should have a very important future

in MR based methodologies examining CBF in relation to cognitive, motor, and sensory challenges.

Positron Emission Tomography (PET)

More than three decades have past since the first two-dimensional PET images were published and modern PET technology continues to provide unique opportunities to examine cerebral metabolism and physiology. PET has enjoyed its most widespread application in the examination of oxygen perfusion (15-O) or cerebral metabolism (FDG), and while these methods remain prominent, PET now allows for tracking of specific neurotransmitters, including chemicals in the dopaminergic, opiate, benzodiazepine, serotonin and cholinergic systems. Separately, laboratories have developed new binding isotopes that provide unique opportunities to track pathophysiological processes. One example of this is the Pittsburgh Compound B (PIB), developed at Pittsburgh Medical Center, that binds to beta amyloid plaques apparent in Alzheimer's disease. This technique provides an important opportunity to characterize of the location and extent of pathophysiological processes associated with Alzheimer's. While PET remains mildly invasive (requiring injection of an isotope) and expensive (requiring access to a cyclotron for atomic acceleration), it still provides methods for specific *in vitro* measures not offered by other techniques.

Magnetoencephalography (MEG)

While there are only a handful of MEG machines in North America, limiting its exposure and application, it remains one of the most exciting new functional neuroimaging techniques with enormous potential that is only beginning to be appreciated. MEG is a measurement of the very small magnetic fields created by electrical activity in thousands of firing neurons (a total signal of less than a hundred-millionth of Earth's magnetic field). In order to detect these tiny field gradients superconducting quantum interference devices (SQUIDs) are used as well as comprehensive shielding from all external magnetic signals. Thus, the design and cost for appropriate equipment required for MEG is not inconsequential. The result, however, is a direct measure of neural firing that combines millisecond

temporal resolution with good spatial resolution (roughly 4-6 mm) to examine sensory, cognitive and motor functioning of the brain. MEG data have been more recently combined with structural MRI data (magnetic source imaging) for making determinations during preoperative assessment and surgical planning in cases of epilepsy. Data thus far have shown MEG to have comparable reliability to intracarotid amobarbital injection (Wada test) for determining language laterality. Clinical applications such as this may help to bring MEG machines into the hospital setting as standard technology allowing for greater clinical and experimental application.

Near Infrared Spectroscopy and Optical Imaging

Near-infrared spectroscopy (NIRS) and optical imaging techniques also offer non-invasive means for monitoring cerebral function through the use of light emitting fibers and detectors. Not dissimilar from photoreceptor plethysmography, near-infrared techniques are based upon the relationship between blood flow and light absorption. Light absorbing compounds, like oxy- and deoxy- hemoglobin naturally vary with blood flow, thus the amount of emitted light returning to the detector is blood flow dependent. While much work is required for NIRS, and more advanced techniques such as optical tomography, to be more widely applicable, there are several very important advantages to these systems. First, most optical imaging systems are highly portable allowing for bedside assessment and off-site use. Second, compared to all other techniques mentioned here, NIRS is a fraction of the cost, with advanced systems for examining optical tomography (e.g., DYNOT system) costing roughly $200,000. Finally, while movement is a primary source of artifact in MRI-based techniques, fluid movement during NIRS data acquisition is permissible allowing for paradigms that include more complicated motor involvement and vocalization. These advantages continue to make NIRS systems very attractive for future clinical and research applications.

Structural Imaging: Diffusion based techniques

Novel structural MRI techniques provide the opportunity to examine cerebral white matter tracts

Functional Magnetic Resonance Imaging in Epilepsy

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Functional magnetic resonance imaging (fMRI) is a noninvasive technique for detecting localized, event-related changes in regional blood flow associated with brain activity. This technique has significant advantages over traditional functional localization methods and is evolving into a useful adjunctive clinical tool in the evaluation of epilepsy surgery candidates. Applications of fMRI in epilepsy include determining hemispheric representation of language and memory functions, predicting side of seizure focus and seizure outcome, studying the nuances of functional reorganization of language and most recently predicting language and memory outcome after left temporal lobectomy.

Methodological advances in functional neuroimaging are enhancing the precision and sophistication of clinical information that can be obtained from fMRI. Improved control and detection of task-correlated movement artifacts and the availability of new higher performance gradient systems operating at 3 Tesla are leading to better signal to noise ratios. Event-related single trial designs provide a means for segregating stimulus trials based on response accuracy. In this way, for example, activation associated with stimuli that are later recalled or recognized can be compared with activation associated with stimuli that are not encoded into memory to better identify systems that support memory functions. New clustered acquisition techniques allow patients to speak in the scanner, enhancing our ability to image spoken language, object naming and category specific aspects of the semantic system. Furthermore, care is being taken to determine test-retest reliability of language lateralization paradigms (Binder, Hammeke, Possing, Swanson, Spanaki, Morris, & Cox, 2001). Finally, awareness is increasing about the importance of monitoring task accuracy while in the scanner and developing appropriate task contrasts other than rest. For example, imagers are moving away from assessing language using covert fluency compared to rest given evidence that rest and visual fixation are active states during which self-initiated linguistic and semantic processes occur (Binder, Frost, Hammeke, Bellgowan, Rao & Cox, 1999; Stark & Squire, 2001).

Language Dominance

The earliest studies of fMRI in epilepsy patients compared language lateralization indexes obtained from fMRI with scores obtained from the intracarotid amobarbital test (IAT). Lateralization indexes (LIs) often are computed for fMRI using the formula $[V_L - V_R] / [V_L + V_R]$, where V_L and V_R are activation volumes for the left and right hemispheres. These studies showed a high degree of correlation (Binder, Swanson, Hammeke, Morris, Mueller, Fischer, Benbadis, Frost, Rao, & Haughton, 1996) and concordance (Desmond, Sum, Wagner, Demb, Shear, Glover, Gabrieli, & Morrell, 1995) between IAT and fMRI in both adults and children (Hertz-Pannier, Gaillard, Mott, Cuenod, Bookheimer, Weinstein, Conry, Papero, Schiff, Le Bihan, Theodore, 1997). fMRI studies using quantitative indexes of language have shown that there is a continuum of language distribution in the brain, with a higher incidence of atypical (bilateral or right) hemisphere language representation in epilepsy patients relative to controls (Springer, Binder, Hammeke,

Swanson, Frost, Bellgowan, Brewer, Perry, Morris & Mueller, 1999). Springer and colleagues (1999) showed that in a group of 50 right-handed epilepsy patients 78% of the epilepsy patients were left hemisphere dominant, 16% had bilateral language and 6% were right hemisphere dominant for language. In contrast, 94% of the 100 right-handed neurologically normal control subjects were left dominant and 6% had bilateral language representation. Moreover, earlier age at onset of brain injury and weaker right-hand dominance were associated with atypical cerebral dominance in epilepsy patients.

While fMRI has been successful for establishing cerebral language dominance, most commonly used language tasks such as semantic decision, reading, covert fluency, and rhyme detection do not result in robust anterior temporal lobe activation, the region typically resected in epilepsy surgery. In an effort to achieve better activation of the dominant anterior temporal lobe, Hammeke and coauthors (2003) developed an auditory descriptive naming activation protocol. This naming task was modeled on findings from an intraoperative stimulation mapping study that showed that auditory naming was disrupted by stimulation to more anterior temporal lobe sites than was visual naming (Hamberger, Goodman, Perrine, & Tamny, 2001). A clustered acquisition scanning protocol was used that allows patients to orally name nouns in response to brief auditory descriptions (e.g., "What a king wears on his head"). This task was contrasted with an auditory discrimination control task that also requires a verbal response. Preliminary findings indicate that the language LIs derived from the descriptive naming protocol are highly correlated with LIs derived from a semantic decision task. Furthermore, the descriptive naming task produced more extensive activation of the anterior temporal lobes than the semantic decision task (Hammeke, Swanson, Possing, Kortenkamp, Kelderman & Binder, 2003).

While further investigation of cases where IAT and fMRI are discordant is needed, fMRI is a reasonable alternative for determining lateralization of language prior to epilepsy surgery. It is not clear whether activation maps from language protocols can be used to guide the resection boundaries since it has not been demonstrated that resection of activated voxels is correlated with language decline.

Language Reorganization

Early onset of epilepsy may result in hemispheric reorganization of language, particularly when the abnormality leading to epilepsy encompasses a large region in the left hemisphere or primary language zones. Age at onset of seizures in the left (n=66) but not the right (n=61) hemisphere has been found to correlate with fMRI language LIs using a semantic decision task (Swanson, Binder, Possing, Hammeke, Sabsevitz, Spanaki, Ruff, Morris, & Mueller 2002). Those with early onset seizures in the left hemisphere have lower LIs indicating more atypical or right hemisphere representation of language. Examination of the group maps suggested that language reorganized to contralateral homologous regions in the frontal and posterior temporal-parietal heteromodal regions but not to temporal regions in those with early left hemisphere seizure onset. Further, patients with left temporal lobe epilepsy and atypical language lateralization had poorer naming abilities than patients with typical left hemisphere dominance. This study suggests that fMRI may elucidate the effects of seizures beginning at different ages on language organization. fMRI can be used to examine not only inter-hemispheric language reorganization, but also intra-hemispheric reorganization. An fMRI study of children who sustained early left hemisphere lesions either adjacent to or remote from classic language regions indicated that function does not always migrate away from lesions (Liegeois, Connelly, Cross, Boyd, Gadian, Vargha-Khadem, & Baldeweg, 2004). Thus, fMRI offers a distinct advantage over IAT for allowing investigators to see the distribution of language organization in pathological states.

Predicting Side of Seizure Focus

Recent studies indicate that fMRI memory activation asymmetries correspond with IAT memory asymmetry scores and that differences in medial temporal lobe activation can be observed based on the side of the seizure focus. Using a complex scene encoding task, Detre and colleagues

Current Functional Neuroimaging Findings in Autism Spectrum Disorders

Cheryl Klaiman, Ph.D. and Robert Schultz, Ph.D.

Autism is a severe developmental disorder characterized by significant impairments in social, behavioral, and communicative functioning. It was first described by Leo Kanner, a child psychiatrist at Johns Hopkins University, in 1943. Though his patients suffered from a wide range of disabilities involving cognitive and language systems, Kanner's description emphasized the social and emotional features of the disorder. Current conceptualizations of the disorder continue to highlight the social-emotional impairments in autism as the core deficit. Both DSM-IV and ICD-10 diagnostic criteria for autism require a triad of deficits that include developmental problems with communication, reciprocal social interaction and repetitive, rigid and stereotypic behaviors. The only unique feature that distinguishes autism from other neuropsychiatric disorders is the deficit in social functioning.

The social, language, and stereotypic behavioral problems that co-occur with autism suggest that the syndrome affects a functionally diverse and widely distributed set of neural systems. However, the affected systems must also be discrete, as autism spares many perceptual and cognitive systems. For example, individuals with autism can have cognitive capabilities within the average range or despite visual-perceptual difficulties in the realm of face processing, might have superior visual-perceptual skills in other domains. Therefore, even though the syndrome likely involves insults to multiple neural systems, it remains possible that the initial insult is localized, leading to more pervasive impairments due to the highly interdependent nature of early developmental processes.

Due to the likely implication of multiple systems being involved in autism spectrum disorders, nearly every neural system in the brain has been proposed at some point as the cause of autism. Which neural system is postulated is typically a result of which aspect of the disorder the researcher deems to be the most salient. For example, those who believe that autism is a result of underlying deficits in complex information processing skills postulate widespread cortical abnormalities sparing early sensory processes as the neural basis of autism (e.g., Minshew, Sweeney, & Bauman, 1997). For those who believe that emotional deficits are the key player towards social difficulties the focus is often on the limbic system (e.g., Bachevalier, 1994; Baron-Cohen et al., 2000; Schultz, Romanski, & Tsatsanis, 2000a). Currently, the research data suggest that select aspects of the temporal and frontal lobes, and portions of the amygdale, are key nodes in systems affected by autism. These data are not yet specific enough to encourage one theory in favor of others. Complicating the matter further is the fact that mental retardation is present in about 70% of individuals with autism, forcing researchers to tease apart causative processes that are specific to autism with the confound of cognitive disability.

A consistent finding within the last few years is that overall brain size appears to be increased by about 5 – 10% in autism (Courchesne et al., 2001; Sparks et al., 2002). However the magnitude of this effect seems to decrease with age (Aylward et al., 2002; Courchesne et al., 2001; Herbert et al., 2003; Kemper & Bauman, 1998; Piven et al., 1995). Conflicting reports exist as to which brain regions are involved or whether all brain regions and systems are equally affected by the expansion. A postmortem study of the cytoarchitecture of the cerebral cortex has been recently conducted and may significantly further our understanding of the disorder (Casanova, Buxhoeveden, Switala, & Roy, 2002). They examined the cortical minicolumns (a basic functional unit) in temporal and frontal tissue of 9 brains of persons with autism and found them to be significantly smaller in width and to have cells which were more dispersed. This pattern could be consistent with a reduction of inhibitory neuronal activity at the boundaries of each column, causing a type of 'cortical noise' and widespread cognitive and behavioral dysfunction. Further, increased brain size might come at the

expense of interconnectivity between specialized neural systems, giving rise to a more fragmented processing structure. Schultz and colleagues (2000b) have suggested that a potential consequence of reduced interconnectivity might be increased modularity and reduced integration of functions. Less neural integration would be consistent with one theory of autism that attributes autistic symptoms to a lack of 'central coherence', a cognitive processing style that results in a difficulty integrating parts into wholes.

The limbic system, especially the amygdala and hippocampus, has generated significant interest in the pathophysiology of autism. The limbic system is located primarily within the medial and ventral region of the temporal lobe. The amygdala, in particular, plays a critical role in emotional arousal, assigning significance to environmental stimuli, and mediating the formation of visual-reward associations or 'emotional' learning (LeDoux, 1996). The amygdala has many afferent and efferent connections to the temporal lobe, forming an important system for mediating the perception of social stimuli. It is thus often highlighted as a core structure in models of autism pathobiology.

Consistent with this theory are postmortem examinations of the brains of persons with autism. Postmortem studies have repeatedly noted abnormalities in the size, density, and dendritic arborization of neurons in the limbic system, including the amygdala, hippocampus, septum, anterior cingulate and mammilary bodies (Bauman, 1996; Kemper & Bauman, 1998). These affected regions are strongly interconnected, and together they comprise the majority of the limbic system. These postmortem findings, therefore, are often heralded as the first good entrance points for understanding the pathobiology of the autism spectrum disorders.

As a result of these findings, there has been great theoretical interest in animal models of autism. Animal models are created through the lesioning of the amygdala of monkeys shortly after their birth. Gradually through the first year of life, these animals develop patterns of behavior reminiscent of autism, including social isolation, lack of eye contact, expressionless faces and motor stereotypies

(Bachevalier, 1994). Similar lesions in adulthood fail to produce these autistic-like symptoms (Emery et al., 2001). However, one recent attempt to replicate these findings with three neonatally lesioned macaque monkeys failed to replicate the autistic type of behaviors found by Bachevalier and colleagues (Prather et al., 2001). At age 8 to 9 months, the monkeys were attentive to social communications, but nevertheless showed a complex pattern of changed social behaviors that included increased fear during dyadic social interactions (Amaral et al., 2003; Prather et al., 2001). Differences in lesioning techniques could explain the results, as well as a difference in rearing environments. This area is clearly very important and more studies are necessary to clarify the effects of early amygdala damage.

Interest in the amygdala also stems from its role in perceptual processing of social stimuli (Adolphs, Tranel, & Damasio, 1998; Castelli et al., 2000; Schultz et al., 2003). In functional neuroimaging studies, hypoactivation of the amygdala has been found during tasks involving the perception of facial expressions and during theory of mind type tasks (Baron-Cohen et al., 1999; Castelli, Frith, Happe, & Frith, 2002; Critchley et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). In addition, functional imaging studies have highlighted brain areas involved in processing pictures of faces. Persons with autism have deficits in their ability to recognize and discriminate faces, and to understand facial expressions. Functional neuroimaging and lesion data show that the fusiform gyrus, a region on the underside of the temporal lobe, is normally engaged during face perception, while neighboring regions in the posterior regions of the middle and superior temporal gyri are important for reading facial expressions and social intent through eye gaze direction. Several fMRI studies have now shown hypoactivation of the fusiform gyrus during face perception tasks (see Figure 1). In a short period of time, this has now become the best replicated finding in the neuroimaging literature (Critchley et al., 2000; Pierce et al., 2001; Schultz et al., 2000a). Further, unlike other brain markers of autism pathobiology, the degree of hypoactivation in the fusiform gyrus is

Neuroimaging of Cognitive Dysfunction in Multiple Sclerosis with Multiple Magnetic Resonance Measures

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Multiple Sclerosis (MS) is a chronic, immune-mediated, demyelinating disease affecting the central nervous system. With a mean onset prior to 30 years of age, (Kurtzke, Page, Murphy, & Norman, 1992) it is one of the most frequent causes of disability in early to middle adulthood (Kurtzke & Wallin, 2000). Cognitive dysfunction is a leading cause of disability in the disorder (Rao et al., 1991b). Persons with MS who are cognitively impaired experience higher rates of unemployment, endure more social isolation, require greater personal assistance, and have greater difficulty with basic homemaking skills (e.g., following recipes), compared with MS patients who are cognitively intact (Rao et al., 1991b).

Approximately half of persons with MS display cognitive impairment on neuropsychological examination (Peyser, Edwards, Poser, & Filskov, 1980; Rao, Leo, Bernardin, & Unverzagt, 1991a). The cognitive dysfunction associated with the disorder is generally more subtle and less severe than that of Alzheimer's disease and other dementias. While individual differences exist, MS is more likely to disrupt some cognitive processes than others (Rao et al., 1991a). MS most commonly leads to deficits in the ability to learn and recall new information. Also frequent are impairments in attention, information processing speed/efficiency and verbal fluency. General intelligence and remote memory are less likely to be affected.

The impact of MS disease processes on the brain varies across individuals and has been assessed by a variety of neuroimaging measures. Early MS research made use of computerized tomography, but this has largely been supplanted by magnetic resonance measures. Cognitive impairment in MS has often been related to lesion measures, including lesion area and lesion volume (Swirsky-Sacchetti et al., 1992; Fulton et al., 1999). Cerebral atrophy may represent a final cumulative effect of different types of MS induced lesions and serve as an important neurobiological marker of disease progression (Jagust & Noseworthy, 2000). Neuropsychological deficits have been associated with measures of atrophy (Swirsky-Sacchetti et al., 1992). Advances in semi-automated and automated techniques allow for improved volumetric quantification of lesions and atrophy, increasing the efficiency and reliability of their measurement. Another trend in neuroimaging research is the use of magnetic resonance spectroscopy (MRS). MRS studies of MS patients reveal decreased levels of the neuron-specific marker N-acetyl aspartate (NAA), thought to reflect axonal damage and loss (Sarchielli et al., 1999). Decreases in NAA, or in the ratios of NAA over creatine (NAA/Cr) or NAA over choline compounds (NAA/Cho), are associated with more advanced disease and higher levels of disability (Sarchielli et al., 1999; De Stefano et al., 2001). Preliminary studies indicate that NAA levels may relate to cognitive variables as well (Pan, Krupp, Elkins, & Coyle, 2001).

My colleagues and I conducted a study to simultaneously assess and compare the relevance of lesion, atrophy, and NAA ratio measures to cognitive performance in MS (Christodoulou et al., 2003). We also sought to determine whether a combination of MR measures could better account for cognitive performance than any individual neuroimaging measure.

Methods

<u>Participants.</u>

The study was approved by the institutional review board for human subject research and all subjects provided informed consent. Participants were 37 individuals with definite MS (Poser et al., 1983) participating in a randomized clinical trial of the safety and efficacy of donepezil in treating cognitive dysfunction. All data were obtained at baseline prior to drug administration (Krupp et al., 2004).

Eligibility criteria included a score at least 0.5 standard deviations (SD) below age and gender based normative data on the Rey Auditory Verbal Learning Test (RAVLT) (Spreen & Strauss, 1998), though the resulting sample tended to perform far less well ($M = -1.5$ $SD = .7$). Patients with severe cognitive impairment on the Mini Mental Status Examination (MMSE < 26) were excluded ($M = 28.5$, $SD = 1.3$) (Folstein, Folstein, & McHugh, 1975). Patients with severe depressive symptoms on the Montgomery-Asberg Depression Scale (MADRS > 14) were also excluded (Montgomery & Asberg, 1979). All participants were ambulatory and had Expanded Disability Status Scale (Kurtzke, 1983) scores of 6.5 or less ($M = 3.8$, range $= 0 - 6.5$, $SD = 1.9$). Concurrent antidepressants, antispasticity agents, and disease-modifying therapies were permitted, so long as dosage had been constant for at least one month prior to the evaluation. Persons currently taking benzodiazepines were excluded. Other exclusion criteria included current alcohol or substance abuse, history of head injury, or other medical condition known to affect cognition.

The MS subjects ranged from 20 to 55 years of age ($M = 44.2$, $SD = 8.1$), with 10 to 20 years of education ($M = 15.0$, $SD = 2.4$). Most were women (81.1%). Most subjects had a relapsing remitting disease course (59.5%), with secondary progressive in the remainder.

<u>Neuropsychological Tests.</u>

A modified version of the Brief Repeatable Battery (BRB) (Rao & Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) formed the core of the testing protocol, and included: Selective Reminding Test (SRT), 10/36 Spatial Recall Test (10/36), Symbol-Digit Modalities Test (SDMT, oral version), Paced Auditory Serial Addition Test (PASAT), and Controlled Oral Word Association (COWA) Category Fluency. BRB tasks are among those most sensitive to MS cognitive deficits (Rao et al., 1991a; Zakzanis, 2000). The Tower of Hanoi was added to the battery to further assess executive functions.

<u>MR Procedures.</u>

MRI/MRS scanning sessions were performed within two weeks of neuropsychological testing on a 1.5 T Marconi Edge whole-body scanner using procedures detailed elsewhere (Christodoulou et al., 2003). The MR procedures consisted of T_1-weighted, T_2-weighted, and FLAIR axial images. A multi-spectral segmentation scheme was applied to both T1- and T2-weighted images for classifying voxels within the mask, resulting in volumes of gray matter, white matter, and cerebrospinal fluid (CSF). The central (ventricular) CSF volume was delineated by both morphology and region growing technologies, beginning with the selection of a central CSF seed. FLAIR images helped distinguish lesions. Central cerebral atrophy was assessed by the percent of central CSF to total intracranial volume. MRS analyses assessed left and right posterior periventricular (PPV) regions. The areas of resonance peaks of NAA, Cr, and Cho were measured, and two ratio measures of interest were calculated: NAA/Cr and NAA/Cho.

Results

Partial correlations between the MR and neuropsychological measures, controlling for age and education, consistently resulted in numerous significant correlations. Central atrophy tended to display some of the largest correlations, accounting for almost half the shared variance with overall neuropsychological performance. Each cognitive task significantly correlated with at least one MR measure. SDMT tended to display some of the strongest correlations with the MR measures. The correlation between SDMT and central atrophy accounted for approximately half the shared variance (partial $r^2 = .484$). Correlations for MRS measures

with cognitive functioning tended to be stronger and more likely to be significant for right versus left hemisphere locations. Lesion volume correlated with all cognitive tasks except the SRT.

A multiple regression analysis assessing the combination of all MR measures correlated more highly with overall neuropsychological performance than individual neuroimaging measures (R = .796, p < .001), accounting for well over half the variance in cognitive performance (R^2 = .634, Adjusted R^2 = .561). To assess the unique contribution of each MR variable, partial correlations of each MR variable with overall cognition were conducted, controlling for age, education, and the other two MR variables. Only the correlation for central atrophy reached significance (partial r = -.531, p = .001), though there were also trends for Right PPV NAA/Cho (partial r = .318, p = .072), and lesion volume (partial r = -.313, p = .076).

Discussion

This sample of MS patients consistently displayed moderate to strong correlations between MR markers of cerebral damage and neuropsychological performance. Among MR measures, central atrophy tended to correlate most highly with cognitive variables. Differences in central atrophy uniquely accounted for differences in overall cognitive performance, even after controlling for lesion volume, NAA ratios, age, and education. Trends were also observed for the unique contribution of NAA and lesion volume variables, suggesting that these would have reached significance in a larger sample. The combination of MR variables was superior to any single measure, accounting for well over half the variance in overall cognitive performance. This supports the view that multidimensional MR models have the potential to serve as powerful measures, and perhaps predictors, of MS evolution (Mainero et al., 2001).

Interestingly, right hemisphere MRS measures correlated more highly with cognition than left sided measures. While the reasons for this pattern are unclear, it is possible that the exclusion of persons with better verbal memory abilities on the RAVLT contributed to the pattern. Earlier research without this screening criterion found a correlation between left sided NAA values and verbal learning/memory performance in MS patients (Pan et al., 2001).

The cognitive task with the single largest correlation with MR measures was the SDMT. As a measure of sustained concentration and information processing speed and efficiency, the SDMT is known to be quite sensitive to brain insult in various neurological populations (Spreen et al., 1998). Other studies in MS have also noted the relative strength of SDMT correlations with MR measures (Hohol et al., 1997).

Among the limitations of this research to date, is its focus on cross sectional data. In future investigations we hope to assess the relevance of neuroimaging to longitudinal changes in cognition.

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agenda than about the people we serve, professional standards erode. "Leaders" that lose focus sometimes look for the lowest common denominator among everyone that calls himself a "clinical neuropsychologist." In 2004 any "leader" who suggests that a clinical neuropsychologist can be adequately prepared by workshops, private reading, without substantial on-site supervision, without clinically focused graduate degrees, or without exposure to a large number of diverse patients undermines our profession's health. Although only a few leaders lose focus, their impact can be substantial. Please do not misunderstand me: the clear majority of our leaders and the vast majority of all clinical neuropsychologists remain focused on serving patients. This majority has consistently promoted the highest professional standards and is justly credited for Clinical Neuropsychology's current stature.

I bring this up because I am weary of watching a small minority of "leaders" driving wedges into our profession by politicizing pseudo-issues: "practice vs. research," "academics vs. practitioners," "collegiality," etc. These actions retard our development. Competent clinicians may not be active researchers, but they are interested in, appreciate, and support the science on which our profession is based. Likewise, competent researchers recognize that their ultimate goal is to advance science in ways that support practitioners and helps patients. When our focus remains on serving patients there can be no acceptance of anything other than "the best."

There are many ways to support and improve our profession, but I'll close with a modest suggestion that, to my knowledge, has not been previously offered: stop re-electing the same people to leadership positions in our various professional organizations. In particular, please stop some of us from "cycling" from the presidencies of one organization to another, and another. This includes me. We have many, many solid and committed colleagues who can, and will, serve us well. Our profession is best served when we open leadership positions to the largest number of people. It's a simple game of numbers. The vast majority of neuropsychologists demand the highest standards for all professional activities: clinical service, research, education, and administration. The wider the door is opened to leadership opportunities the more likely it becomes that effective leaders will be found to serve all of us - but most of all to serve our patients.

Am I an "elitist?" You be the judge. To my way of thinking, it isn't elitist to serve patients by expecting the most from oneself, one's leaders, and one's profession. Every person that wants to join us should be given an equal opportunity to do so. But I also expect "the most" from those that choose this career. If this makes me an "elitist," then so be it.

I greatly appreciate the trust that you have placed in me by allowing me to serve as your president. There are a lot of good people out there to get involved and who will further our profession. I hope you take the opportunities that lay before you and make the most of your chances.

End of sermon from this bully pulpit.

motor functions usually attributed to the frontal lobes (Bilder et al., 1995; Szeszko et al., 2002).

These results are exciting in that they provide detailed mapping of diagnostic group effects across the entire surface of the cortex and hippocampal formation. Similar mapping methods may be applied to virtually any brain structure. These mapping methods can also capitalize on virtually *any categorical or continuous variable*. Thus, while we have shown in these examples how we can map diagnosis effects on the cortical and hippocampal surface, and the related publications already show how effects of other variables such as sex and age can also be mapped onto these surfaces as covariates, we are now entering an exciting phase of research where we are mapping other measures, including detailed measures of neuropsychological performance, directly onto these surfaces. We will therefore soon produce maps that show how key variables, such as scores on specific measures of memory, attention, and executive functions, relate to alterations in cortical and hippocampal surface anatomy. Our preliminary analyses already have revealed distinctive patterns of cortical gray matter deficit in the prefrontal cortex that appear to characterize patients with limited clinical response to novel antipsychotic treatment. So far, analyses of structure-function relations have often been limited to manual morphometry of a given "region of interest" segmented from the rest of the brain using more or less arbitrary landmarks, and examining correlations of the volumes of these "chunks" of tissue with other functional variables. While potentially useful, such analyses may miss important anatomic detail. The new analyses we are conducting will show the detailed local changes in surface structure that correspond to the wide-ranging functional deficits in schizophrenia. It is hoped that in the process we will gain further insights into the functional anatomic bases of schizophrenia. Similar methods are already being applied to examine other important characteristics of schizophrenia (for example, the presence of specific genetic and disease effects (Cannon et al., 2002)), and to the mapping of abnormalities in diverse neuropsychiatric syndromes

and to track normal developmental changes in brain structure (Ballmaier et al., 2004; Sowell et al., 2004; Thompson et al., 2004c; Thompson et al., 2004a; Thompson et al., 2004b). We anticipate that the availability of these powerful new methods will lead to a more mature view of individual differences in brain structure and how these differences relate to both normal development and disease.

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Division 40 Listserv Information

Division 40 offers three listservs that are open to all interested individuals. To join a list, send an e-mail message to listserv@lists.apa.org. The subject line should be blank. The message should read: SUBSCRIBE Listname First Last [substitute the name of the list you wish to join and your own first and last names]. For example, if Jane Brain wishes to join the ANNOUNCE listserv, she would write SUBSCRIBE DIV40ANNOUNCE Jane Brain.

- DIV40ANNOUNCE is an announce-only list created to allow members to receive information from the Division about divisional activities and advocacy efforts relevant to clinical neuropsychology
  The list administrator is Paula K. Shear, Ph.D.: paula.shear@uc.edu

- DIV40EMA is a discussion forum for the Division 40 Ethnic Minority Affairs Interest Group, which focuses on professional development for neuropsychologists and students who are members of ethnic minority groups as well as the promotion of culturally competent research and practice among all neuropsychologists
  The list administrators is Jovier Evans: jevans2@iupui.edu
  The EMA group is chaired by Drs. Monica Rivera-Mindt and Tony Wong: riveramindt@fordham.edu and twong@unityhealth.org

- DIV40WIN is a discussion forum for the Division 40 Women in Neuropsychology Interest Group, which focuses on professional development of women and efforts to increase the representation of women in leadership positions.
  The list administrator and WIN chair is Dr. Cynthia Kubu: kubuc@ccf.org

by estimating localized diffusion of water. For example, magnetic transfer imaging, was developed in 1989 in order improve contrast between subcortical white matter and cortical gray matter. This technique capitalizes on the transfer of magnetization between pools of free water protons and pools of protons bound to a macromolecule (such as myelin). MTI provides a "magnetic transfer ratio", or MTR, which is the ratio of magnetization moving between these bodies of protons. Thus, an increased transfer ratio is indicative of greater volumes of healthy white matter tracts. The primary difference afforded by MTI compared to traditional MRI is its increased sensitivity to the range of potential relaxation times, which permits more detailed analysis of non-water components in brain tissue, such as myelin.

More recently, Diffusion Tensor Imaging (DTI) has created significant excitement within the neuroscience community for its capability to provide exquisite images of the white matter tracts in the brain. In principle, DTI measures the diffusion of water throughout the brain, with areas of dense white matter having greater directional diffusion (a measure referred to as fractional anisotropy) than areas of lower white matter density. Water diffusing equally in all directions, such as in CSF, is isotropic and restricted diffusion of water, such as that occurring within axons, is anisotropic. DTI not only provides unparalleled images of cortical and subcortical white matter tracts, but with advanced analyses the opportunity to examine models of connectivity between cortical areas. Thus, images not only outline the white matter bundles, but also the direction of propagation (e.g., left to right, anterior to posterior, inferior to superior). Theoretically, these data can be compared against functional maps providing the unique opportunity for examining the relationship between multiple points of brain activation and the axonal tracts that connect them. Thus, DTI provides the opportunity to examine the interface between structural and functional connectivity models which may enhance our understanding of the distributed neural networks responsible for specific behaviors.

Metabolism: Magnetic Resonance Spectroscopy

MRS provides important information about the neurometabolic status of the brain and, in some instances, has proven to be more sensitive to pathology than structural imaging. MRS is based on the same basic physical principles employed in conventional MR sequences, however, its signal is not derived from water or lipid. Signals arising in MRS are produced by hydrogen nuclei in macromolecules producing distinct local magnetic environments. That is, each measured nuclei maintain discrete orientations when placed within the MRI field and can be localized, catalogued, and quantified. The MRS signal is typically displayed as a spectrum of waves and the primary signals of interest arise from N-acetylaspartate (NAA), creatine/phosphocreatine (Cre), choline-containing compounds (Cho), glutamate (Glu), and lactate. Clinical application of MRS has been widespread including acute and chronic application to TBI and several studies examining *normal appearing white matter* in multiple sclerosis. Advanced software for spectra analysis such as LCModel has provided new opportunities to examine lactate and glutamate levels following severe brain trauma in order to monitor secondary effects of ischemia and hyperglycolysis. MRS data may now be acquired in single voxel, multi-voxel, or whole brain analyses. There remains enormous potential for integrating information about cerebral metabolism with structural and functional imaging data. MRS provides an important opportunity to do so.

Conclusion

It is an extraordinary time for the development and application of novel neuroimaging techniques and, as these techniques proliferate, validation of their use for examining behavior in clinical samples will be paramount. Functional neuroimaging now dominates research within the cognitive neurosciences and, by further integrating neuroimaging methods into its training and practice, neuropsychology will capitalize upon the opportunity to make a unique contribution to neuroscience. Ultimately, neuroimaging holds the promise of directly linking observable human

behavior to the underlying constituents of brain structure, physiology, and function. For this promise to be realized, it will be critical for neuropsychology to guide the application of the current and the next generation of novel neuroimaging techniques to clinical samples.

(1998) demonstrated that activation asymmetries in the posterior medial temporal region corresponded with the results of IAT memory assessment. In another study, Swanson and colleagues used a complex scene encoding task that results in bilateral hippocampal activation in normal individuals and found that activation asymmetries in the anterior hippocampus in epilepsy patients correlated with hippocampal volume asymmetries (Swanson, Sabsevitz, Spanaki, Hammeke, Possing, Bellgowan, Morris, Mueller, & Binder, 2001). Thus, it appears that fMRI memory activation asymmetries have both functional (IAT) and structural correlates (hippocampal volumes).

fMRI memory studies have been used to predict side of seizure focus. Using a remote memory task that involved recollection of a hometown walking route, greater medial temporal activation was found contralateral to the seizure focus and this activation classified the seizure focus in 90% of epilepsy patients (Jokeit, Okujava, & Woermann, 2001). In another study, greater activation in the left medial temporal lobe (hippocampus, parahippocampal gyrus and collateral sulcus) during a semantic encoding task was found in patients with right compared to left temporal lobe epilepsy (Bellgowan, Binder, Swanson, Hammeke, Springer, Frost, Mueller, & Morris, 1998). In a large series, Binder and colleagues showed that fMRI activation asymmetries in the hippocampus correctly predicted side of seizure focus in 50 of 66 epilepsy patients (76%) and was relatively equivalent to IAT memory testing in accuracy (Binder, Bellgowan, Swanson, Hammeke, Possing, Kelderman, McKiernan, Mueller, & Morris, 2001). In a study where novel and repeating stimuli (patterns, faces, words and scenes) were contrasted, greater medial temporal lobe activation was seen contralateral to the seizure focus in nine patients (Golby, Poldrack, Illes, Chen,

Desmond & Gabrieli, 2002). Finally, a recent study compared two different fMRI protocols (i.e., semantic decision and definition naming tasks) to IAT memory testing in identifying side of seizure focus (Sabsevitz, Swanson, Hammeke, Possing, Phillips, Spanaki, Raghavan, Morris, & Binder, in press). These investigators found that activation asymmetries in the hippocampus in response to the definition naming protocol were relatively equivalent in accuracy (21/27 patients or 78% accurate) to IAT memory testing (22/27 patients or 85% accurate) using an optimal asymmetry cutoff score.

Similar to language reorganization studies, fMRI can be used to examine intrahemispheric reorganization of memory. Using a verbal episodic memory task, patients with left hippocampal sclerosis were found to have decreased parahippocampal activation and greater dorsolateral frontal activation (Dupont, Van de Moortele, Samson, Hasboun, Poline, Adam, Lehericy, Bihan, Samson, & Baulac, 2000). One study found that functional memory asymmetries predict seizure outcome one year after surgery (Killgore, Glosser, Casasanto, French, Alsop, & Detre, 1999). Similar to results of IAT studies, recent work with memory paradigms or using medial temporal or hippocampal regions of interest show that fMRI memory activation patterns can be used to lateralize seizure foci and predict memory outcome after anterior temporal lobectomy (ATL).

Predicting Cognitive Outcome

The use of fMRI activation asymmetries for predicting cognitive outcome after ATL represents an exciting new development in functional neuroimaging. In one of the first studies to address this issue, Sabsevitz and colleagues (2003) examined the clinical utility of preoperative fMRI and Wada language testing for predicting postoperative changes in confrontation naming abilities following left ATL. Twenty-four patients with left temporal lobe epilepsy who underwent preoperative fMRI language mapping and Wada language testing and both pre- and 6-month post-operative neuropsychological testing were examined. Preoperative fMRI language mapping used a

semantic decision paradigm that has previously been shown to produce highly reliable and strongly left-lateralized activation patterns in areas implicated in language processing (Binder, Frost, Hammeke, Rao, Cox, Prieto, 1997; Frost, Binder, Springer, Hammeke, Bellgowan, Rao, & Cox, 1999). The results from this study showed that the degree of language lateralization, as measured by both fMRI and Wada testing, significantly predicted naming outcome. That is, the greater degree of language lateralization toward the surgical hemisphere was associated with greater postoperative decline on the Boston Naming Test (see figure 1). fMRI showed 100% sensitivity and 73% specificity in predicting significant naming decline (i.e., > 2 SD decline as compared to a right ATL control group), while Wada language testing showed 92% sensitivity and 45% specificity. The findings from this study suggest that fMRI could be used to stratify patients in terms of risk, potentially allowing patients and physicians to more accurately weigh the risks and benefits of surgery.
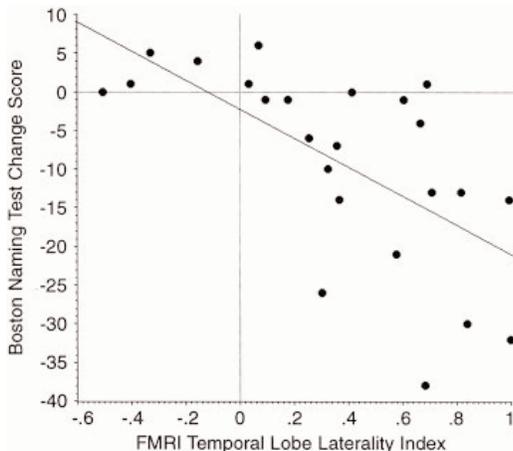

Figure 1. The relationship between fMRI language LI and Boston Naming Test change score after left ATL.

There is also some evidence to suggest that preoperative fMRI can predict memory outcome following epilepsy surgery. In a study by Richardson and colleagues (2004), an incidental verbal encoding task (i.e., classify words as "living" or "nonliving") was used in the scanner prior to surgery to predict verbal memory outcome in a small group (n = 10) of left ATL patients. Results showed that the degree of preoperative activation asymmetry in the hippocampus predicted the amount of decline

on several verbal memory measures following surgery. Also, the fMRI task was found to be a better predictor of verbal memory outcome than pre-operative memory performance or left hippocampal volume. In another study, Rabin and colleagues (2004) used the preoperative activation patterns associated with a complex visual scene-encoding task to predict changes in performance on the same task 6 months following surgery. It was found that the degree of activation asymmetry in the medial temporal lobe prior to surgery predicted changes in task performance following ATL. Finally, Sabsevitz and colleagues (in press) used a semantic encoding task to predict memory outcome in a large group (n = 49) of left ATL patients and found that the fMRI task was a better predictor of verbal memory outcome than other known risk factors, such as age at seizure onset, preoperative memory performance, and lateralization of IAT memory scores.

The demonstrated predictive validity of fMRI data for language and memory morbidity is a powerful new pre-surgical use for fMRI.

Case Example[1]

The patient is a 28-year-old right-handed female with a history of medically intractable seizures since age two following prolonged febrile seizures. Prior to surgery, she experienced two to six complex partial seizures per week. Seizure semiology was characterized by an aura of nausea and unusual abdominal sensations followed by alteration in consciousness, bilateral pill-rolling hand automatisms, progressing to right hand posturing and lip smacking, followed by post-ictal language impairment. Long-term video EEG monitoring revealed ictal and interictal abnormalities in the left temporal region. MRI of the brain conducted prior to surgery was normal, with no evidence of increased signal in the left hippocampus as would be expected with mesial temporal sclerosis. Pre-operative neuropsychological testing was consistent with dominant hemisphere dysfunction showing verbal intellectual abilities in the Borderline range (Verbal Comprehension Index = 78) and nonverbal intellectual abilities in the Average range (Perceptual Organization Index = 108). Verbal memory was in the average range while nonverbal memory was in

the high average to superior range. Object naming abilities were impaired, consistent with her early onset of seizures in the left hemisphere.

IAT revealed strong left hemisphere dominance for speech and language functions. On memory testing, there was a significant memory asymmetry in the incorrect direction. That is, in the inject right/test left condition, the patient recognized 8 of 8 objects that were presented during the period of hemianesthesia. However, in the inject left/test right hemisphere condition, she recognized only 1 of 8 objects presented during the period of hemianesthesia. Thus, results of memory testing indicated little to no capacity to form new memories in the hemisphere contralateral to the seizure focus, raising concerns about risk for post-operative amnesia. Given the unexpected findings with regard to memory, the IAT was repeated. During the second IAT, the patient did not become fully hemiplegic following injection of the left hemisphere despite administration of additional doses of amytal. The patient recognized 8 of 8 objects presented following injection of both the left and right hemispheres. The second IAT was considered invalid and the patient was considered at risk for significant post operative memory decline.

The patient was referred to the Medical College of Wisconsin for functional localization of memory using fMRI. A visual scene encoding task alternating with a visual discrimination control task was used to evaluate memory lateralization. Activation in the anterior hippocampus was strongly left-lateralized (Memory LI = 90), consistent with the results of the first IAT indicating little memory capacity in the right hippocampus.

Despite these results, the patient underwent a left ATL at an outside facility. Neuropsychological testing was conducted 6 months following surgery with results showing mild naming decline (See Table 1) and significant memory morbidity.

In this case, two different IAT memory results were obtained, though the second IAT, showing memory function contralateral to the seizure focus, was thought to be invalid. fMRI confirmed this result, as hippocampal activation during a scene encoding task was strongly left-lateralized. In this case, IAT and fMRI were concordant and both predicted the poor memory outcome that occurred following left ATL.

Conclusion

While considerable progress has been made in the design and interpretation of fMRI studies of language and memory, we are not prepared to abandon IAT. IAT has the methodological advantage of being an inactivation procedure and the practical advantages of not being limited by level of cognitive functioning, body habitus (obesity, head size, neck length) or claustrophobia. The time limitations and invasive aspects of IAT represent significant limitations. fMRI provides adjunctive information on lateralization and detailed information about functional localization. However, the extent to which activated voxels represent networks critical for the performance of a cognitive activity, associated incidental activation that is not critical to the function of interest, or non-task-specific functions that were not fully "subtracted out" is unclear. Currently, we rely on fMRI for lateralization of language and memory for surgical planning in cases where an IAT cannot be performed safely or IAT results are ambiguous. Finally, examination of fMRI activation in specific regions of interest and with tailored testing protocols offers a

Table 1. Object naming and verbal list learning scores before and after left ATL.

	Preoperative		Postoperative	
	Raw Score	Range	Raw Score	Range
Selective Reminding Test				
Learning Across Trials	51	Average	29	Impaired
Long-term Storage	50	Average	7	Impaired
Consistent Long-Term Retrieval	38	Average	2	Impaired
Delayed Recall	9	L. Average	4	Impaired
Boston Naming Test (60-item)	39	Impaired	30	Impaired

more powerful method for functional localization and for predicting language and memory outcome.

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Dementia: A Multidisciplinary Update

26th Annual Conference of the New York Neuropsychology Group;
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strongly correlated to degree of social disability (Schultz et al., 2001). These data and related work showing that the fusiform gyrus is engaged by theory of mind type tasks (Castelli et al., 2000; Martin & Weisberg, 2003; Schultz et al., 2003) suggest that the principal pathology in autism resides in limbic regions, and that disturbances in social-affective orientation early in life cause a cascade of neurodevelopmental events, including the failure to develop perceptual expertise for faces and for visual and auditory displays of emotion. In addition to the fusiform and amygdala, posterior aspects of the superior temporal sulcus (STS) might be implicated in autism spectrum disorders. The STS is involved in perception of dynamic social signals, such as facial expressions, social gestures and interpretation of direction of eye gaze (Allison, Puce, & McCarthy, 2000; Schultz et al., 2003).

Aspects of frontal lobe integrity and function have also been implicated in the pathogenesis of autism. Older studies using lower resolution neuroimaging techniques reported general hypoactivation of the frontal lobes. Functional neuroimaging data collected in the last decade are converging to show that subregions of the prefrontal cortices with especially strong connectivity to limbic areas are critical for 'social cognition', that is thinking about other's thoughts, feelings and intentions. These deficits are common in individuals with autism. Theory of mind ability has been linked to functional activity in the medial region of the superior frontal gyrus (primarily Brodmann area 9) and to prefrontal cortex immediately above the orbits of the eyes, the orbital frontal cortex. Functions in these prefrontal regions appear to be disrupted in persons with autism spectrum conditions. A study using positron emission tomography (PET) reported reduced dopaminergic activity in the medial prefrontal cortex of individuals with autism (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997). Reduced glucose metabolism has also been reported
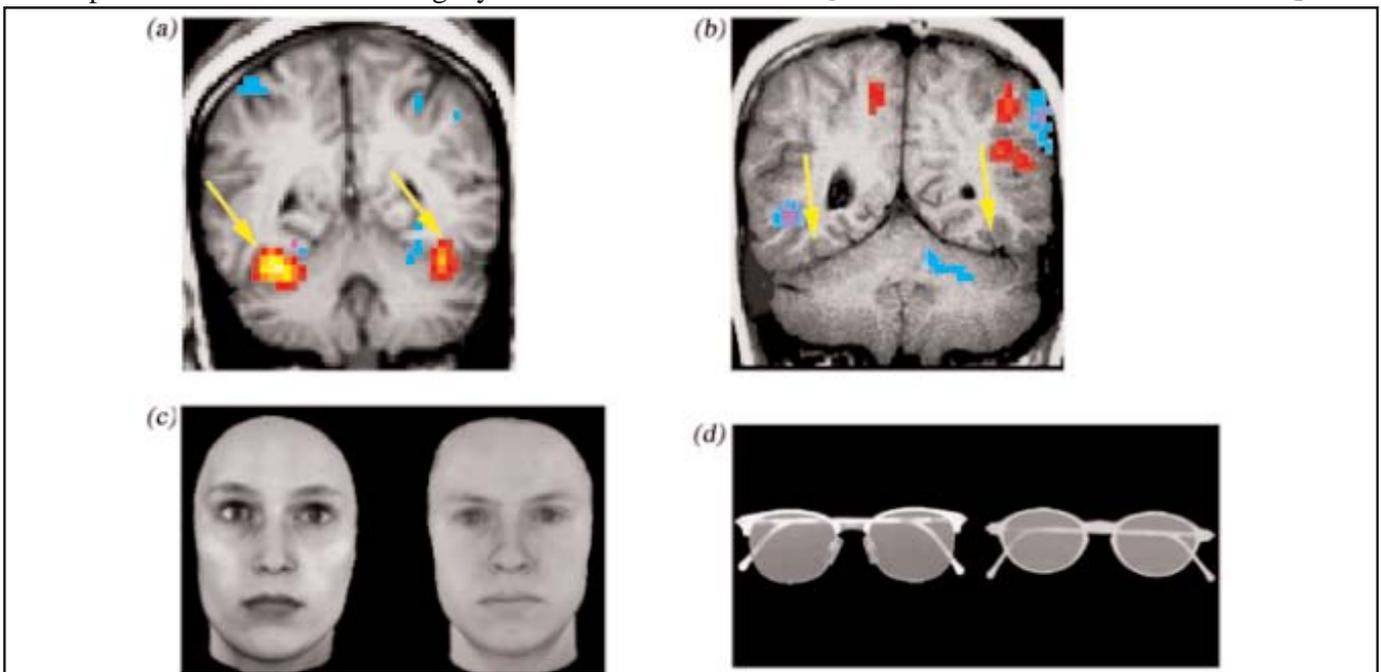

Figure 1

Functional MRIs of the Brain During Face Perception. The fusiform face area is shown in red/yellow (arrows) in (a) a young adult with autism and (b) a matched normal control. In the control, there is a clear focus of face-related activation bilaterally in the fusiform gyrus along the ventral surface of the temporal lobe. Contrast this with the lack of activation in the fusiform gyrus in the young adult with autism. Images are in a coronal orientation, with right and left hemisphere reversed by convention, and functional data is superimposed on anatomical images for localization. fMRI data are from a blocked experiment comparing (c) face perception to (d) non-face object perception during a "same/different" discrimination task on a 1.5 Tesla system, the threshold for displaying activations is set at t = 1.5. Object specific areas are shown in blue on the fMRI maps.

in a subdivision of the anterior cingulate gyrus in persons with autism engaged in a verbal memory task (Haznedar et al., 2000). Moreover, nonhuman primate studies have documented abnormal social responsivity and loss of social position within their social group following lesions to orbital and medial prefrontal cortices. The orbital and medial prefrontal cortices have dense reciprocal connections with the amygdala providing the architecture for a system that can regulate social-cognitive processes. A parallel set of amygdala-cortical circuitry in the temporal lobes focuses on social-perceptual processes. It is thus possible that autism is largely caused by abnormalities in both of these amygdala-cortical loops.

In summary, the major findings on the neural basis of autism involve abnormalities in brain size, and in aspects of the limbic system and functionally related and connected regions of the orbitomedial prefrontal cortex, and visual association areas of the temporal lobe. Much continued research into the underlying brain mechanisms is currently underway, though there is still much work to be done. Functional neuroimaging techniques are revolutionizing psychiatry and systems level neuroscience, and ultimately it should enable researchers to define dynamic brain processes that give rise to each specific symptom and feature of autism. A continuing challenge is to adapt *in vivo* neuroimaging techniques so that they can be used with much younger children and infants. Understanding the underlying brain processes in younger children is likely a prerequisite for a truer understanding of the neural basis of autism as the disorder develops over time within the first few years of life. Moreover, the initial onset of deficits in social skills is likely to pave the way for the deficits seen in more complex social skills, which in turn is likely to develop into lifelong neurostructural and neurofunctional abnormalities.

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Annual Meeting Of Rehabilitation Psychology Conference

Division 22 (Rehabilitation Psychology) and the American Board of Rehabilitation Psychology (ABRP), Inc. are sponsoring the 7th Annual Rehabilitation Psychology 2005 Conference, to be held April 8-10, 2005 at the Wyndham Baltimore Inner Harbor Hotel in Baltimore Maryland. This conference features ABRP preparation workshops for ABPP, American Congress of Rehabilitation Medicine-Brain Injury-Interdisciplinary Special Interest Group Presentations, and a student scientific poster competition. A panel of professional presenters will offer educational seminars on topics including traumatic brain injury, stroke, spinal cord injury, pediatric rehabilitation, diversity issues in rehabilitation practice, alternative rehabilitation methods, and rehabilitation research, with seminars approved for CE credit. Abstracts for posters are due to Dr. Thomas Martin by February 1, 2005. Hotel reservations may be made at 1-800-Wyndham or direct 410-385-6700. Please request the Rehabilitation Psychology group rate. For more information, contact Dr. Joseph H. Hinkebein at 573-882-8847 or at hinkebeinj@health.missouri.edu. Poster submittal information can be obtained from Dr. Martin at martinta@health.missouri.edu.

Announcement

Last year, the Practice Advisory Committee and Science Advisory Committee of APA convened a task force for which the primary goal was to establish a consensus statement regarding the role of neuropsychologists in the clinical use of functional magnetic resonance imaging (fMRI). This effort was particularly timely, as organizations such as the American Medical Association and the American Academy of Neurology have been working to develop CPT codes and RVU's for these procedures.

The official position statement was approved by the Division 40 Executive Committee in July 2004 and is published in The Clinical Neuropsychologist (Official Position of the Division of Clinical Neuropsychology (APA Division 40) on The Role Of Neuropsychologists In Clinical Use Of fMRI: Approved by the Division 40 Executive Committee, July 28, 2004, Volume 18, Number 3 / July 2004 pp. 349-351). Members of the task force include: *Julie Bobholz (Chair), Bob Bilder, Susan Bookheimer, Michael Cole, Allan Mirsky, Neil Pliskin, Steve Rao, Joe Ricker, Andrew Saykin, John Sweeney, Mike Westerveld.* As a follow-up to this position paper, task force members are planning to develop core competencies / training standards for neuropsychologists interested in doing clinical fMRI.