-Poster Session 1-

Test-retest reliability of task fMRI across 3 sessions in patients with mild cognitive impairment

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As the aging population grows, it has become increasingly important to carefully characterize amnestic mild cognitive impairment (aMCI), a preclinical stage of Alzheimer's disease (AD). Functional magnetic resonance imaging (fMRI) is a valuable tool for monitoring disease progression in selectively vulnerable brain regions associated with AD neuropathology. However, the reliability of fMRI data in longitudinal studies of older adults with aMCI is largely unexplored. To address this, amnestic aMCI participants completed two visual working tasks, a delayed-recognition task and a one-back task, on three separate scanning sessions over a three-month period. Test-retest reliability of the fMRI blood oxygen level dependent (BOLD) activity was assessed using an intraclass correlation (ICC) analysis approach. Results indicated that brain regions engaged during the task displayed greater reliability across sessions compared to regions that were not utilized by the task. During When brain regions Duringtask-engagement, differential reliability scores were observed across the brain such that the frontal lobe, medial temporal lobe, and subcortical structures exhibited fair to moderate reliability (ICC = 0.3 – 0.6), while temporal, parietal, and occipital regions exhibited moderate to good reliability (ICC = 0.4 – 0.7). Additionally, reliability across brain regions was more stable when three fMRI sessions were used in the ICC calculation relative to two fMRI sessions. In conclusion, the fMRI BOLD signal is reliable across scanning sessions in this population and thus a useful tool for tracking longitudinal change in observational and interventional studies in aMCI.

Neural Activation During the Encoding of Negative Material Predicts Change in Symptomatology in Major Depressive Disorder

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Considerable research indicates that depressed individuals have better memory for negative material than do nondepressed individuals, and that this bias is driven by differential patterns of neural activation. It is not known, however, whether neural activation patterns that occur during encoding of affective stimuli can be used to predict the course of depression. Using functional magnetic resonance imaging (fMRI), we

examined whether change in depressive symptoms could be predicted by patterns of neural activation that underlie negative memory biases. Depressed participants viewed negative and neutral pictures during fMRI scanning at baseline and completed an incidental memory task for these pictures one week later. Severity of depression was assessed both at baseline (Time 1) and at Time 2, an average of 18 months later, using the Beck Depression Inventory II (BDI-II). Contrast maps of activation for subsequently remembered negative versus subsequently remembered neutral pictures were regressed against change in BDI-II scores from Time 1 to Time 2, controlling for initial symptom severity. Results of this analysis revealed no associations between amygdala response at encoding and subsequent change in depressive symptoms, or between memory sensitivity for negative stimuli and symptom change. In contrast, however, whole brain analyses revealed significant positive associations between changes in depressive symptoms and neural activation in the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) during the successful encoding of negative pictures. These findings indicate that neural activation in these areas of the brain during encoding is a better predictor of long-term symptomatic outcome than is memory sensitivity for negative material.

Medial temporal lobe involvement in learning to retrieve math facts.

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When children first learn to solve arithmetic problems they use elaborate counting strategies. With concerted practice, children learn to rapidly retrieve math facts from memory. Almost nothing is known about the neural basis of this process in school-age children. In this study, we used a cognitive training paradigm and fMRI to investigate arithmetic fact learning in 3rd and 4th grade children. Twenty-two children trained for 6 days by solving 14 problems over 70 times each. Problems were double- plus single-digit addition problems (e.g., 9 + 47 = 56) which are unlikely to be retrieved prior to training. Indeed, initially children reported retrieving answers 20% of the time, but after training were retrieving answers over 70% of the time, and reaction times improved substantially, from 5.3 to 1.9 seconds. During fMRI scanning, children were presented with trained as well as novel problems which were matched for difficulty (sets counterbalanced across participants). Compared to trained problems, untrained problems elicited greater activity in the bilateral intraparietal sulcus (IPS), dorsolateral prefrontal cortex, anterior insula and left lateral occipital cortex. In contrast, trained problems produced greater activity in bilateral angular gyrus, hippocampus, middle temporal gyrus and left parahippocampal gyrus. Furthermore, functional connectivity analysis revealed that during novel problem solving the right IPS had greater connectivity with the left IPS and visual cortex, while during trained problems the right IPS showed greater connectivity to the parahippocampal gyrus and hippocampus. Together these results highlight the dynamic assembly of neural circuits underpinning arithmetic fact learning in children.

Modulation of default mode network activity by the knowledge of observation

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It is well established that the default mode network (DMN) activates when individuals are at rest. However, there has been considerable heterogeneity in participant instructions across studies of the resting state—in particular, in the degree to which participants were made aware that they were being observed. Our goal in this study was to elucidate how resting state activity depends on knowledge of being watched.
We used two distinct manipulations to address this question: first, we described two separate scans as being either anatomical or functional, when in fact both were functional; and second, in a putatively separate experiment, we informed participants that we were able to observe the contents of their thoughts, and after a more thorough description of the anatomical/functional distinction, carried out three more functional scans, one of which was again described to the participant as anatomical.
Our results demonstrate systematic differences across several networks as a function of these instructional manipulations. Most strikingly, there was decreased functional connectivity between DMN-associated areas when comparing the second set of scans to the first, and increased activity across a range of non-DMN regions.
These results suggest that the mere awareness that one is being observed causes significant changes in the patterns of activity across a range of functional networks, including the DMN. They also highlight the importance of using precise instructions in resting-state studies, because even slight variations in instruction can substantially affect resting brain activity.This research was supported by the Institute for Collaborative Biotechnologies under grant W911NF-09-D-0001.

Results From A National Memory Screening Day For The Detection of Dementia In Community-Based Populations

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The Alzheimer's Foundation of America (AFA) is a national nonprofit organization with more than 1,600 member organizations that focuses on providing optimal care to

individuals with Alzheimer's disease and related illnesses and their families. In response to under-diagnosis and misdiagnosis of Alzheimer's disease, AFA holds an annual National Memory Screening Day (NMSD) in collaboration with local healthcare professionals and organizations nationwide. The free screenings promote early detection of memory problems and appropriate intervention. Data from 4396 participants in NMSD 2010 were analyzed. Overall, 11.7% of participants failed one of the eight standard dementia screening tests. No significant differences in screening failure rates were found across the eight standardize screening tests ($p>.05$). As expected, a gradual increase in dementia screening failure rate was found with increasing age ($p<.05$) and decreasing educational attainment ($p<.05$). No significant interaction was found between age and education. Analysis of participants' subjective memory complaints suggested that this measure could provide a reliable indication of subsequent performance on the dementia screening tests. Thus, when participants were asked if they were "concerned about their memory" their answers were predictive of their dementia screening outcome ($p<.007$). However, when asked if they were "more forgetful these days", results were not predictive of their screening outcome. Overall, these results inform the design of effective dementia screening programs for the detection of dementia in community based populations.

Effect of Schizophrenia on Dorsolateral Prefrontal Cortex Function and Theta-Band Power during Selective Long-Term Memory Encoding

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Selective encoding of episodic memories requires increased cognitive control in environments filled with task irrelevant information. Patients with schizophrenia have reduced cognitive control and struggle to ignore irrelevant stimuli during such selective encoding tasks. The current fMRI and EEG experiments examined whether these problems with selective encoding can be linked to dorsolateral prefrontal cortex (DLPFC) dysfunction and reduced theta band power (~4-8 Hz). The Context Maintenance Encoding Task (CMET) requires participants to make living/nonliving judgments to words under two encoding conditions: (1) "Fixed Rule" – make living/nonliving judgment and remember all words. (2) "Variable Rule" –make living/nonliving judgment and remember "target" (T) words only. In the fMRI version of the task targets were defined visually (i.e., same color of word and surrounding border), and in the EEG task targets were defined auditorially (i.e., either matching male or female voice). The fMRI CMET task included 30 controls and 21 patients and showed greater DLPFC activation in controls relative to patients when participants were required to ignore irrelevant information (i.e., non-target vs. target contrast). The EEG CMET task was performed on

a separate sample of 26 controls and 27 patients. When the same contrast was performed (non-target vs. target) there was an increase in theta band power in controls that was reduced in patients. These combined results suggest that DLPFC dysfunction and reduced theta power contribute to patients' difficulty ignoring task irrelevant information during selective encoding tasks under high cognitive control conditions.

Mesolimbic Activity Tracks Preference Change in the Mere Exposure Effect

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Objective: The mere exposure effect is one of the most replicated phenomena in psychology. It describes the fact that preferences for sensory stimuli increase with exposure. However, neuroimaging studies have failed to identify differences in brain reward areas associated with preference change. We hypothesized that this resulted from the use of temporally constrained designs in which neural adaption obscured the exposure effect.
Methods: We developed a protracted experimental design spanning ten days. In a first session, subjects provided ratings for two novel liquids and then tasted the liquids while undergoing fMRI. Subjects then consumed and provided daily ratings for one of the juices. In a second session, subjects again tasted both liquids while undergoing fMRI and provided final ratings.
Results: Behavioral ratings indicated that preference for the repeated liquid increased relative to that of the non-repeated liquid. A cluster in the ventromedial prefrontal cortex showed a greater change in activation across sessions for the repeated relative to the control liquid. Further, the magnitude of behavioral preference change predicted differences in neural activity in the VTA and dorsal/central striatum.
Conclusions: The mere exposure effect demonstrates that the reward value of stimuli is not fixed, but changes with experience. These findings present a challenge for reinforcement learning models that assume fixed reward values are used to calculate prediction errors in the VTA and striatum. Additionally, these findings point to a plausible neuronal account for behavioral addictions in which repetition, not pharmacological manipulation, leads to maladaptive reward learning.

The effects of anticipatory stress on associative memory retrieval.

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Our ability to store and retrieve memories allows us to access knowledge about the past to inform decisions and actions in the present. The process of recollecting specific, associative details about past events involves engagement of frontoparietal attentional control mechanisms. However, when confronted with a stressful situation, controlled processing is often impaired, and activity in these frontoparietal networks disrupted. Here, we investigated whether acute anticipatory stress, operationalized by threat of shock, might influence memory retrieval processes. To the extent that associative source retrieval requires attentional control, we hypothesized that such tasks will be vulnerable to interference under conditions of stress relative to safety. During encoding, images of faces were paired with either object or place associates. At retrieval, subjects (N=24) viewed old and new face cues while we recorded physiological measures (i.e., skin conductance, heart rate) and neural activity with electroencephalography (EEG); if subjects identified the face as old, they were asked to recollect the paired associate. In general, stress during retrieval did not influence face-only recognition. Critically, associative memory was selectively affected under conditions of stress; more specifically, face-object associations were impaired by anticipatory stress, while face-place associations were unaffected. Event-related potential (ERP) EEG analyses revealed reduced source recollection responses in frontal and parietal regions during a late time window for threat relative to safe blocks. Together, these findings suggest that stress disrupts controlled processing related to retrieval of associative information.

Neural correlates of recollection and familiarity deficits in schizophrenia

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Long-term memory deficits in schizophrenia are central to the disorder and highly predictive of functional outcome. A recent review indicated that schizophrenia patients exhibit a large deficit in recollection and a medium deficit in familiarity. Given that studies in healthy individuals have demonstrated important roles for the hippocampus in recollection and the perirhinal cortex in familiarity, it is possible that disrupted functioning in these regions contributes to recollection and familiarity deficits in schizophrenia. To reveal the neural bases of these retrieval deficits, the current study used fMRI to identify group differences in brain activity during encoding of stimuli that were subsequently recollected or judged to be familiar. Patients and demographically matched healthy controls were scanned during encoding of novel word pairs. After scanning, they completed an associative recognition test, making recognition confidence judgments for each intact and recombined word pair. Behavioral analysis indicated that both recollection and familiarity were impaired in patients, in line with previous findings. fMRI results revealed that patients exhibited hypoactivation of a network of regions including the hippocampus during encoding of word pairs that were later recollected. Furthermore, subsequent familiarity for word pairs was associated with increased activation of a network of regions including the perirhinal cortex in schizophrenia

patients compared to controls. These preliminary results provide the first evidence for dissociable medial temporal lobe correlates of recollection and familiarity deficits in schizophrenia, and suggest that memory deficits in schizophrenia are related to disrupted modulation of both the perirhinal cortex and hippocampus.

Body Mass and White Matter: The Influence of Vascular and Inflammatory Markers

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Objective: High adiposity is deleteriously associated with brain health, and may disproportionately affect white matter integrity; however, limited information exists regarding the mechanisms underlying the association between body mass (BMI) and white matter integrity. The present study evaluated whether vascular and inflammatory markers influence the relationship between BMI and white matter in healthy aging.
Methods: Cross-sectional evaluation of white matter integrity, BMI, and vascular/inflammatory factors in a cohort of 139 healthy older adults (mean age: 71.3 years). Participants underwent diffusion tensor imaging, provided blood samples, and participated in a health evaluation. Vascular risk factors and vascular/inflammatory blood markers were assessed. The primary outcome measure was fractional anisotropy (FA) of the genu, body, and splenium (corpus callosum); exploratory measures included additional white matter regions, based on significant associations with BMI.
Results: Regression analyses indicated that higher BMI was associated with lower FA in the corpus callosum, cingulate, and fornix ($p<.001$). Vascular and inflammatory factors influenced the association between BMI and FA. Specifically, BMI was independently associated with the genu [$\beta=-.21$; $B=-.0024$; 95% CI, -.0048 to -.0000; $p=.05$] and cingulate fibers [$\beta=-.39$; $B=-.0035$; 95% CI,-.0056 to -.0015; $p<.001$], even after controlling for vascular/inflammatory risk factors and blood markers. In contrast, BMI was no longer significantly associated with the fornix and middle/posterior regions of the corpus callosum after controlling for these markers.
Interpretation: Results partially support a vascular/inflammatory hypothesis, but also suggest a more complex relationship between BMI and white matter characterized by potentially different neuroanatomic vulnerability.

Does Chemotherapy Alter Visuospatial Working Memory: An fMRI Study

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Working memory impairments are a commonly self-reported complaint from cancer patients after chemotherapy. The most studied memory modality in this population is verbal working memory, yet visuospatial abilities, important in everyday functioning, have been revealed as being different between breast cancer (BC) patients and healthy controls prior to chemotherapy commencement (Scherling, 2011). This study follows-up with an investigation of post-treatment brain activation patterns related to visuospatial working memory.

BC patients and individually-matched non-cancer controls underwent functional magnetic resonance imaging prior to- and after- chemotherapy as they performed a visuospatial working N-back task. fMRI task error rates and reaction times, as well as neuropsychological assessments, hospital records, and salivary biomarkers were also examined. fMRI images were pre-processed and examined using SPM8, thresholded at $p_{crit} < 0.001$ with a cluster-level $pFWE\text{-}corr < 0.05$.

Patients, post-chemotherapy, showed more neural activity in the right insula compared to controls. Depression, anxiety and reaction time modulated this activation pattern. Patients showed more activity in several brain regions post-chemotherapy compared to pre-treatment, including the right frontal lobe and left parietal/temporal gyri. Regression analyses revealed an opposite group relationship between activations and reaction time, with controls revealing decreased activity with longer reaction times and patients showing increased activity with slower responses. Additionally, depression and fatigue contributed to patterns of brain activity.

Results indicate that chemotherapy impacts neurophysiology during visuospatial working memory but that this is also accompanied by the impact of mood. Patients consistently reveal increased neural activity compared to controls, possibly explaining patient's cognitive fatigue and reported memory complaints. As well, increased insular activations in patients compared to controls could be the consequence of the anterior insular misattributing emotional salience to mundane events (Menon and Uddin, 2010). While the task stimuli themselves are not emotionally charged, they could be perceived as such with a self-imposed pressure to perform in light of increased post-treatment cognitive complaints.

Age-dependent Failure in Neurogenesis in Mouse Models of Down Syndrome

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Down syndrome is characterized by significant degeneration of the hippocampal region particularly the dentate gyrus that plays a crucial role in contextual learning. This area undergoes significant degeneration in people with Down syndrome and its mouse models. To test whether degeneration of dentate gyrus in mouse models of Down syndrome is a result of failed neurogenesis, we studied the status of neurogenesis in Ts65Dn and Ts1Rhr mouse models of Down syndrome. The Ts65Dn mouse model has segmental trisomy of mouse chromosome 16 (Mmu16) that encompasses a region between Znf295 to Mrp139. Ts1Rhr mice have three copies of almost 1/3 of genes that are triplicated in Ts65Dn mice. Multiple studies have shown a significant reduction in BRDU-positive neurons in the Ts65Dn mice. However, not all BRDU-positive cells will eventually differentiate into neurons. For this reason, we studied the status of doublecortin-positive cells in the dentate gyrus in 3-months and 6-months old Ts65Dn and Ts1Rhr mice to their respective 2N controls. Similar to our recent findings (Dang et al., 2013), we found a significant age-dependent loss of doublecortin-positive cells in 2N and Ts65Dn mice but not in Ts1Rhr mice. This suggests that triplication of a segment of Mmu16 between C21orf18 to Pred22 is responsible for the significant loss of neurogenesis in Ts65Dn mice. Interestingly, App and Sod1 genes are found in this segment and are not triplicated in Ts1Rhr mice. Currently, we are testing the effects of triplication of these genes on neurogenesis in Ts65Dn mice.

Neural substrates underlying the effects of post-encoding stress and emotional arousal on recollection and familiarity.

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Stress and emotional arousal are both known to affect learning and memory. For example, memory for emotional images tends to be stronger than memory for neutral images, an effect that appears related to enhanced amygdala and medial temporal lobe (MTL) activity during encoding. Stress has been shown to enhance and impair memory in different situations, and these effects can interact with emotion arousal. Previous work has also demonstrated a relationship between neural activity during encoding and subsequent memory performance. Here we tested the novel hypothesis that this relationship between neural activity during encoding and subsequent memory is modulated by post-encoding stress. Functional magnetic resonance imaging data were collected while subjects incidentally encoded negative and neutral pictures; then half of the subjects were stressed using an ice-water cold-pressor procedure. Recognition memory confidence was tested after a 24-hour delay to examine recollection and familiarity. We found that post-encoding stress decreased recollection-based recognition, particularly for negative pictures, but did not affect subsequent familiarity-based recognition. Whole-group neuroimaging results suggest that activation of MTL regions was related to subsequent memory, and that amygdala activity was more strongly related

to subsequent memory for emotional images than to memory for neutral images, whereas parahippocampal activity was more strongly related to memory for neutral images. Preliminary between-group analyses revealed that the brain regions where encoding activity predicted subsequent recollection differed between the stress and control groups. These results could reflect a stress-induced modulation of memory consolidation processes.

-Poster Session 2-

Anodal Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex Enhances Multitasking Performance

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Undertaking two or more tasks at a time is ubiquitous in our daily living. Although multitasking is not beyond human ability, task performance is deteriorated when we execute multiple tasks simultaneously. Previous studies have suggested an important role of dorsolateral prefrontal cortex (DLPFC) in multitasking processes, however, direct causal evidence is lacking. To address this, twenty-nine healthy young adults (aged 18-35 years) received anodal transcranial direct current stimulation (tDCS) to their left DLPFC prior to engaging in a 3-D video game designed to assess multitasking performance. Participants were separated into three subgroups: real-sham (i.e., those who received real tDCS in the first block, followed by sham tDCS in the second block, conducted one hour later), sham-real (those who received sham tDCS first, followed by real tDCS in the second block one hour later) and sham-sham (those who received sham tDCS in both blocks as control). Results revealed that real-sham participants showed improved multitasking performance in the second block when compared to the first block. Interestingly, no significant changes were found between the first and second blocks in the sham-real or the sham-sham (control) groups. The findings imply that anodal tDCS over left DLPFC induced delayed after-effects which enhanced multitasking performance 1 hour after the stimulation.

In the face of distraction: dopaminergic modulation of fronto-striatal circuitry during working memory

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Dopamine has long been implicated in the online maintenance of information across short delays. Specifically, dopamine has been proposed to modulate the strength of working memory representations in the face of intervening distractors. This hypothesis has not been tested in humans. We fill this gap, using pharmacological neuroimaging. Healthy young subjects were scanned after intake of the dopamine receptor agonist bromocriptine or placebo (in a within-subject, counterbalanced and double blind design). During scanning, they performed a delayed match-to-sample task with face cues. A face or scene distractor was presented during the delay period (between the cue and the probe). Bromocriptine decreased distractor-resistance, such that it impaired performance after face relative to scene distraction. This decrease in distractor-resistance was accompanied by drug-induced disruption of delay-period activity in the prefrontal cortex, as well as drug-induced disruption of functional connectivity between the prefrontal cortex and the fusiform face area. These results provide the first empirical evidence for the pervasive, yet hitherto untested hypothesis that dopaminergic modulation of the prefrontal cortex alters resistance of working memory representations to distraction. Moreover, we show that the effects of dopamine on the distractor-resistance of these representations are accompanied by modulation of the functional strength of connections between the prefrontal cortex and stimulus-specific posterior cortex.

Distributed Attention Training in Young Adults

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Attention is fundamental to our ability to navigate the complex sensory input we face day-to-day and effectively engage in goal-directed activities. We have developed a spatial attention task on multiple platforms to assess the ability to focus and distribute spatial attention based on varying the amount of cued information about where a target will appear. The goal of the current study was to test, using an adaptive training version of this paradigm ("DAT"), whether individuals can train and improve their spatial attention abilities. Healthy young adults who trained on this paradigm were given a central spatial cue, with varying degrees of information, indicating where in space on the screen a go/no-go target was going to appear. The participant played this task for 10 days over 2 weeks, 30 minutes a day for a total of 5 hours training. An age-matched group of controls played a non-cognitive task for the same training duration. All participants played the

DAT assessment with EEG prior to and following training. Participants completed a battery of cognitive assessments as outcome measures to test for cognitive transfer induced by training. We found that training on the paradigm improved participant's focused and distributed attention abilities; i.e. response time significantly improved over all information conditions on the assessment (0% information, 50% information, 75% information, and 100% information), whereas the control group exhibited no improvement. Participant's who trained on DAT got significantly better at the selective attention component measures in Useful Field of View, and improved performance on the Visual Search paradigm in both Top-Down and Bottom-up components, where as controls did not. Importantly, there was no difference in improvement between groups in a simple reaction time test, demonstrating that this was an influence on attention, not just processing speed. These results suggest that spatial attention can be trained using this paradigm and should be evaluated as an effective treatment for attention deficits.

Neural Underpinnings of Reasoning: Double Dissociation in Left Parietal Cortex

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Numerous studies implicate a lateral frontoparietal network in relational reasoning. We sought to examine more closely the parietal contribution. We measured task-related fMRI activation in a set of parietal regions of interest that had been defined previously by their patterns of structural and functional connectivity with other brain regions (Mars et al., 2011). Data were drawn from 22 young adults who had performed a relational matching task that requires 1st-order and 2nd-order relational reasoning—based on semantic knowledge in one test and visuospatial analysis in another (Wendelken et al., 2011). Results showed visuospatial domain specificity in all parietal regions, despite faster reaction times and higher accuracy in that domain ($p<.0001$). Select regions were sensitive to the distinction between 1st- and 2nd-order relational processing, especially in the visuospatial domain. A double dissociation in left inferior parietal lobule (demonstrated in a 4-way interaction, $F[1,21]=16.765$, $p<.0001$) showed that relational integration is supported by posterior regions associated with complex attention and memory processes. Functional selectivity for 2nd-order relational processing was exhibited in left angular gyrus (AG), one of two regions identified as being tightly connected to left rostrolateral PFC (Mars et al., 2011). These results, along with lesion data (Baldo et al., 2010), indicate that left inferior parietal lobule plays a central role in relational reasoning; and may extend a model of AG as a site where multisensory inputs are combined to support complex cognition (Seghier, 2013) to include a uniquely human (Mars et al., 2011), long-range AG-rostrolateral PFC connection associated with relational reasoning.

Cortical dynamics of fast learning and cognitive training in patients with schizophrenia

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An emerging hypothesis in the neuropathology of schizophrenia is that alterations in oscillatory activity contribute to cognitive and behavioral symptoms prevalent in the disorder. Here, we use magnetoencephalographic imaging (MEG-I) to test the hypothesis that impoverished oscillatory activity over frontal cortices impedes skill learning in a group of patients with schizophrenia undergoing cognitive training. MEG data was collected using a 275-channel biomagnetometer (VSM MedTech) during a modified serial reaction time task (SRTT). Individuals were instructed to respond to a short vowel (/e/, /i/, /o/, /u/) presented in the auditory domain at the beginning of each trial. Subjects either responded by speaking the vowel they have heard, or pressing a button corresponding to one of four spatial locations. Sitmulus trains were either presented randomly or in an eight-step movement sequence. Behaviorally, impairments in both vocal and manual motor sequence learning were observed in the patient group. MEG-I data was reconstructed using an adaptive spatial filtering technique in the beta (12-30Hz), gamma (30-55Hz), high gamma (65-90Hz) and ultra-high gamma (90-115Hz) range. During the response phase, an increase in high-gamma power localized to bilateral frontal cortex in healthy controls around movement onset. In patients with schizophrenia, this oscillatory power was reduced during the same points in time. Changes in beta power remained uncompromised in the patient group during both vocal and manual skill learning. This data indicates that impairments in recruiting high-frequency neural synchrony translates into a deficit in cognitive learning at a rapid pace. These neuroimaging-based markers have the potential to track recovery following cognitive-based rehabilitative paradigms.

Monetary decision making in behavioral variant frontotemporal dementia and Alzheimer's disease

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Objective: To investigate the cognitive mechanisms underlying poor decision making in patients with behavioral-variant frontotemporal dementia (bvFTD). We hypothesized that bvFTD patients would exhibit diminished loss aversion relative to Alzheimer's disease (AD) patients and normal controls (NC).

Background: Poor decision making is common in neurodegenerative disease, and particularly salient and disruptive in bvFTD, where poor financial decisions and overspending are often cited.
Methods: We studied bvFTD (n=15; mean age=59.9; mean MMSE=26.6), AD (n=14; mean age=71; mean MMSE=24.9), and NC (n=21; mean age=70.6; mean MMSE=29.5) performance on an experimental economics task measuring individual sensitivity to financial losses. Participants were endowed with $30 and asked to accept or reject 36 two-outcome gambles with win:loss ratios ranging between 0.6 and 2.2. Loss aversion (lambda) is determined by the win:loss threshold for choosing to gamble. Data were analyzed using a general linear model with age, MMSE, and CDR score as covariates.
Results: bvFTD had significantly lower lambdas relative to AD ($p < .001$) and controls ($p < .05$). ADs and controls did not differ from each other. Follow-up analyses in a subset of subjects with executive function scores (n=39) showed that the difference between bvFTD and AD remained significant after controlling for executive functioning.
Conclusions: bvFTD subjects exhibited significantly less loss aversion than AD subjects and NC, even after controlling for executive functioning. This study provides evidence of dissociable decision making mechanisms in bvFTD and AD, as there is a pattern of loss aversion that is maintained in AD and NC that is lost in bvFTD.

White matter integrity of the eye-movement network of an antisaccade task in healthy, older adults

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Brain aging is accompanied by changes in cognitive functioning and may be a risk factor for neurodegenerative disease. A better understanding of the mechanisms of age related cognitive impairment would help to determine which individuals would most benefit from early therapeutic interventions to prevent dementia and how normal aging contributes to cognitive decline. The most common age-related changes in cognition occur in executive function, which has been associated with elevated risk for decline in cognitive and functional performance associated with the onset of dementia (Blacker et al., 2007; Fine et al., 2008; Royall et al., 2004; Kramer et al., 2007). A useful tool in measuring executive function is the antisaccade (AS) task. The AS task is strongly correlated with impairments in executive function (Nieman et al., 2000; Hutton et al., 2004; Boxer et al., 2006) that occur with normal brain aging (Mirsky et al., 2011; Hellmuth et al., 2012). We investigated the white matter integrity of the cortical oculomotor network involved in AS task performance by using diffusion tensor imaging (DTI), which is a method that allows for the measurement of white matter fiber tracts in vivo based on the diffusivity of water in the white matter of the brain. Tractography in

key regions in the AS eye-movement network were revealed to be important in predicting AS performance in older adults.

Increased CSF neurofilament reflects disease severity in Frontotemporal degeneration

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Objective: Cerebrospinal fluid (CSF) neurofilament light chain (NfL) concentration, thought to be a marker of axonal damage, is known to be elevated in neurological disorders including frontotemporal degeneration (FTD). We investigated the clinical correlates of elevated CSF NfL levels in FTD.
Methods: CSF NfL, amyloid-β42 (Aβ42), tau and phosphorylated tau (ptau) concentrations were compared in 47 normal controls (NC), 8 asymptomatic gene carriers (NC2) of FTD-causing mutations, 79 FTD (45 behavioral variant frontotemporal dementia [bvFTD], 18 progressive nonfluent aphasia [PNFA], 16 semantic dementia [SD]), 22 progressive supranuclear palsy, 50 Alzheimer's disease, 6 Parkinson's disease and 17 corticobasal syndrome patients. Additional analyses were done in a subset of 44 biomarker enriched FTD cases. Correlations between CSF analyte levels were performed with neuropsychological measures and the Clinical Dementia Rating scale sum of boxes (CDRsb). Voxel-based morphometry of structural MR images determined the relationship between brain volume and CSF NfL.
Results: Mean CSF NfL concentrations were higher in bvFTD, SD and PNFA than other groups. NfL in NC2 was similar to NC. Mean CSF NfL, but not other CSF measures, positively correlated with CDRsb in FTD, and not in other diagnostic groups. In FTD, grey and white matter volume negatively correlated with CSF NfL concentration, such that individuals with highest NfL levels exhibited the most atrophy.
Interpretation: CSF NfL is elevated in symptomatic FTD and correlates with disease severity. This measurement may be a useful surrogate endpoint of disease severity in FTD clinical trials. Longitudinal studies of CSF NfL in FTD are warranted.

Anodal Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex Enhances Multitasking Performance

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Undertaking two or more tasks at a time is ubiquitous in our daily living. Although multitasking is not beyond human ability, task performance is deteriorated when we execute multiple tasks simultaneously. Previous studies have suggested an important role of dorsolateral prefrontal cortex (DLPFC) in multitasking processes, however, direct causal evidence is lacking. To address this, twenty-nine healthy young adults (aged 18-35 years) received anodal transcranial direct current stimulation (tDCS) to their left DLPFC prior to engaging in a 3-D video game designed to assess multitasking performance. Participants were separated into three subgroups: real-sham (i.e., those who received real tDCS in the first block, followed by sham tDCS in the second block, conducted one hour later), sham-real (those who received sham tDCS first, followed by real tDCS in the second block one hour later) and sham-sham (those who received sham tDCS in both blocks as control). Results revealed that real-sham participants showed improved multitasking performance in the second block when compared to the first block. Interestingly, no significant changes were found between the first and second blocks in the sham-real or the sham-sham (control) groups. The findings imply that anodal tDCS over left DLPFC induced delayed after-effects which enhanced multitasking performance 1 hour after the stimulation.

The Neural Correlates of Hypothesis Formation and Evaluation

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Research on split-brain, delusional, and stroke patients suggests that the left hemisphere concocts stories, or hypotheses, to explain unexpected events and the right hemisphere evaluates these hypotheses. The goal of this study was to localize the neural substrates of hypothesis formation and evaluation in healthy individuals. Based on studies of inference making and deductive reasoning, we predicted that the left dorsal medial prefrontal cortex (dmPFC) supports hypothesis generation, and that either the right dmPFC or right inferior PFC supports hypothesis evaluation, as these areas are associated with conclusion validation and belief-logic contradiction. In this study, we recorded subjects' brain activity with fMRI as they attempted to generate appropriate category labels for a series of word sets. We used novel word sets that were designed to either elicit hypothesis formation and evaluation ("ad hoc" word sets) or automatic processing ("automatic" word sets). Based on our assumption that subjects create and verify hypotheses to a greater extent 1) during the period before generating a possible label and 2) during ad hoc

trials, we looked for differential brain activity in ad hoc trials vs. automatic trials and TRs before vs. after label generation. Consistent with our predictions, both contrasts revealed increased activity in the left dmPFC, right dmPFC, and left vlPFC, which we attribute to hypothesis formation, hypothesis evaluation, and memory retrieval, respectively. Our results provide a focally specific neural explanation for the behaviors associated with split-brain and delusional patients. This research was supported by the Institute for Collaborative Biotechnologies under grant W911NF-09-D-0001.

Thinking left versus thinking right: Is there a left-hemisphere advantage for relational reasoning?

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The goal of the current study was to explore the distinct contributions of the left and right hemispheres to relational reasoning through lateralized visual field presentation. Healthy young adults performed one of two visuospatial tasks that required relational integration: a relational matching task that can be considered a simple form of analogical reasoning or a test of transitive inference. Pairs of visual stimuli were presented rapidly in either the left or right hemifield as participants maintained central fixation, thereby isolating encoding to the contralateral hemisphere. A comparison of accuracy for left-hemisphere, right-hemisphere, and mixed-hemisphere trials revealed an important role for the left hemisphere in both tasks. The right hemisphere played an important role only when processing necessitated the reorganization of relational information. In summary, we observed significant differences in the ability to integrate or compare individual relations as a function of the hemisphere that initially encoded the relations.

Genetic variants in longevity gene *KLOTHO* are associated with increased brain volumes in aging

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Identification of genetic variants associated with brain structures in aging may elucidate new biologic mechanisms underlying resilience to age-dependent cognitive decline and identify regions critical to healthy aging. Two variants in *KLOTHO* (*KL*), rs9536314 (F352V) and rs9527025 (C370S), segregate together and form a haplotype (KL-VS)

associated with longevity and protection from cardiovascular disease in heterozygous carriers. Since brain size decreases with age, we sought to determine whether carrying one copy of the protective KL-VS allele is associated with larger gray matter (GM) volumes in healthy aging individuals. Using VBM, we performed unbiased whole-brain analysis in a cohort of 217 healthy older adults (mean±SE 70.2±0.5years). Using linear regression models adjusted for total intracranial volume, age, sex, education, and APOE ε4 status, we found KL-VS haplotype was associated with greater volumes of frontal cortical regions. After adjusting for multiple testing, one of the strongest associations was greater GM volume of right dorsolateral prefrontal cortex (DLPFC, MaxT=4.55, P_{FWE}=0.03), a finding that replicated in an independent cohort of 224 healthy older adults (81.2±0.5years, P=0.04). Because right DLPFC is important for executive function, we analyzed working memory and processing speed in individuals of both cohorts. By meta-analysis, greater executive function was associated with carrying the KL-VS haplotype (beta=0.39±0.11, P=0.0003), and volume of right DLPFC correlated with increased executive function in both cohorts (P=0.03). These results identify genetic variation in *KLOTHO* as a potential determinant of DLPFC volume, confirm the involvement of the right DLPFC in executive function, and implicate klotho in mechanisms of healthy cognitive aging.