

Title: Regional Cerebral Blood Flow studies of object perception, identification, localization, and memory.

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Principal Investigator

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Total requested accrual
4100 Healthy Volunteers

Project Uses Ionizing Radiation: ☒ No ☐ Yes (*attach RSC/RDRC documentation*)

- ☐ Medically-indicated only
- ☐ Research-related only
- ☐ Both

IND/IDE ☒ No ☐ Yes (*attach FDA documentation*)

Drug/Device/# _____

Sponsor: _____

Durable Power of Attorney ☒ No ☐ Yes

Multi-institutional Project ☒ No ☐ Yes Institution#1 _____ FWA

Date of IRB approval _____ (*attach IRB documentation*)

Data and Safety Monitoring Board ☒ No ☐ Yes

Technology Transfer Agreement ☒ No ☐ Yes

Agreement type and number _____ Expiration Date _____

Samples are being stored ☒ No ☐ Yes

Flesch-Kincaid reading level of consent form: _____ 9.1 _____

Precis

Objective:

Our goal is to study the functional organization of the intact human brain by combining cognitive tasks and neuroimaging. Functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) will be used to measure brain activity in healthy human subjects engaged in performing cognitive tasks. These tasks will address specific questions concerning the neural systems that mediate perception, attention, memory, decision-making, emotion, plasticity and social interactions. fMRI and MEG, respectively, will be employed to investigate the spatial and temporal aspects of these neural systems.

Study Population:

Normal volunteer participants aged 18-65, who are in good general health will be recruited from the local community and studied under this minimal risk protocol.

Design:

Subjects will perform cognitive tasks in behavioral and/or neuroimaging sessions (fMRI or MEG).

Outcome Measures:

Behavior as performance on cognitive tasks, and brain activity (fMRI and MEG) will be combined to yield information about the neural correlates and processes underlying different aspects of human cognition including visual perception, memory, learning, emotion, social cognition, decision-making and attention.

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List of Abbreviations

AFNI: Analysis of functional neuroimages
ANOVA: Analysis of variance
ASL : Arterial spin labeling
BOLD : Blood oxygen level dependent
CBF : Cerebral blood flow
DLPFC: Dorsolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex
DTI: Diffusion tensor imaging
DWI : Diffusion weighted imaging
EEG: Electroencephalography
EPI : Echo planar imaging
fc-MRI: Functional connectivity magnetic resonance imaging
FDR : False discovery rate
FEF: Frontal eye fields
FFA : Fusiform face area
FG : Fusiform gyrus
FIR : Finite impulse response
fMRI : Functional magnetic resonance imaging
FsFast : FreeSurfer functional analysis stream
GLM : General linear model
HRF : Hemodynamic response function
Hz: Hertz
IAPS : International affective picture system
IFC : Inferior frontal cortex
IPL : Intraparietal lobule
IPS : Intraparietal sulcus
LBC : Laboratory of brain and cognition
LIP : Lateral intraparietal area
MATLAB: Matrix laboratory
MDS : Multi-dimensional scaling
MEG : Magnetoencephalography
MFG : Middle frontal gyrus
MOG: Middle occipital gyrus
MPRAGE: Magnetization prepared rapid gradient echo
MRI : Magnetic resonance imaging
ms: milliseconds
MT : Middle temporal
MVPA: Multi-voxel pattern analysis
PASL : Pulsed arterial spin labeling
PCASL: Pseudo-continuous arterial spin labeling
PET: Positron emission tomography
PLS: Partial least squares
PPA : Parahippocampal place area
PTSD : Post-traumatic stress disorder

ROI: Region of interest
rs-fcMRI: Resting state functional connectivity magnetic resonance imaging
rs-fMRI: Resting state functional magnetic resonance imaging
RT : Reaction time
rt-fMRI: real time functional magnetic resonance imaging
SAE : Serious adverse event
SAM : Synthetic aperture magnetometry
SENSE: Sensitivity encoding
sMRI: Structural magnetic resonance imaging
SEF: Supplementary eye fields
SFS: Superior frontal sulcus
SNR : Signal to noise ratio
SPGR : Spoiled gradient recalled echo
STS: Superior temporal sulcus
T : Tesla
TBI : Traumatic brain injury
TPJ : Temporoparietal junction
TR : Repetition time
UF : Uncinate fasciculus
VMPFC: ventromedial prefrontal cortex
VTC : Ventral temporal cortex

1. Introduction

The long-term goal of these studies is to understand the neural mechanisms underlying cognitive processes, including perception, attention, emotion, learning and memory, especially in the sensory modality, decision-making, plasticity and moral and social cognition. For clarity, we have grouped our investigations in 7 themes, and presented a general introduction to each theme in this section. Background, rationale and significance of each experiment are listed along with the primary objectives in the study objectives section. The 7 themes are as follows:

A. Attention:

The visual system is usually confronted with cluttered scenes consisting of many different objects. Because the capacity of the visual system to process multiple stimuli at any given time is limited, objects must compete for neural representation. One way to resolve this competition is by spatially directed attention, which facilitates information processing at one location by efficiently filtering out interfering information from distracting objects at nearby locations. In our prior fMRI studies, and in parallel single-unit recording experiments (Luck et al., 1997; Reynolds et al., 1999, 2000; Fries et al., 2001, Desimone & Duncan, 1995; Kastner, Deweerd, Desimone, & Ungerleider, 1998), we have found that competition among multiple stimuli is evidenced by the mutual suppression of their visually evoked responses (Kastner et al., 1998), which occurs most strongly at the level of the receptive field (Kastner et al., 2001). In addition, our fMRI studies have shown that biasing signals due to selective attention can modulate neural activity in visual cortex not only in the presence of visual stimuli, but also when one anticipates their appearance (Kastner et al., 1999). Although our monkey lesions studies have indicated that the competition among stimuli for representation is ultimately resolved within visual cortex itself (De Weerd et al., 1998, 2003), the source of top-down biasing signals likely derives from a distributed network of areas in the frontal and parietal lobes (Corbetta et al., 2000; Hopfinger et al., 2000; Kastner et al., 2000; Friedman-Hill et al., 2003; Kincade et al., 2005). This biased competition model of attention (Desimone and Duncan, 1995) has guided much of our work over the past ten years. Covert attention can influence this competition in a goal-driven top-down manner often referred to as endogenous attention, or in a stimulus-driven bottom-up manner, termed exogenous attention. A major focus of our work under this theme is to understand the sources of top-down signals that bias competition in visual cortex and the specific roles they may play in directed attention. In addition, we are interested in how bottom-up signals can drive the re-orienting of attention in an exogenous fashion. Further, we plan to study the role of attention, both endogenous and exogenous, in the process of perceptual learning. In addition, we plan to study the sources and natural time course of “sustained attention,” the act of focusing on a single task for an extended period of time. Methodological difficulties have complicated researchers’ picture of sustained attention, making it difficult to observe without affecting it (Smallwood & Schooler, 2006). We are interested in how recent advances fMRI data collection and analysis might be employed to give a clearer picture of this universal human experience on a single-trial basis.

B. Decision-making

Decision-making may be defined as the process of choosing a preferred option or course of action from among a set of alternatives. In decision-making models based on Bayesian inference (Kersten et al., 2004), there are typically three variables: 1) the accumulation of sensory evidence in favor of one over another alternative; 2) the probability of occurrence of the two alternatives,

based on prior knowledge; and 3) the anticipated reward value of selecting one over another alternative. Motivated by results from single-unit recordings in monkeys (for review, see Gold and Shadlen, 2007), we have undertaken fMRI experiments designed to investigate the neural mechanisms for decision-making processes in the human brain. In these studies, we plan to manipulate: a) sensory evidence via degraded images of stimuli and b) decision criteria via either changes in prior probability or anticipated reward.

Based on neurophysiological studies in monkeys performing sensory discriminations (e.g., Newsome et al., 1989; Shadlen and Newsome, 2001; de Lafuente and Romo, 2003; Romo and Salinas, 2003), it has been proposed that perceptual decisions are made by integrating the difference in spike rates from pools of neurons selectively tuned to the different perceptual choices (Gold and Shadlen, 2002). For example, in a direction-of-motion task in which the monkey must decide whether a noisy field of dots is moving upward or downward, a decision can be formed by computing the difference in responses between populations of neurons in area MT sensitive to upward motion and those sensitive to downward motion (e.g., Gold and Shadlen, 2000, 2002). Further, this computation appears to occur in the lateral intraparietal area (LIP) and the dorsolateral prefrontal cortex (DLPFC). Similarly, in a somatosensory task in which the monkey must decide which of two vibratory tactile stimuli has a higher frequency, a decision can be formed by subtracting the activities of two populations of somatosensory (SII) neurons that prefer high and low frequencies, respectively (Romo et al., 2003). Again, this subtraction operation in monkeys appears to occur in the DLPFC.

In a recent fMRI study (Heekeren et al., 2004), we showed that even in humans, when subjects perform a complex face-house categorization task, the left superior frontal sulcus (SFS) of posterior DLPFC, is involved in computing perceptual decisions, by comparing outputs from face-responsive fusiform face area (FFA) and house responsive parahippocampal place area (PPA). As a next step in this research topic, we would now like to ask whether other Bayesian variables such as prior probability and reward are also represented in the brain, and if so, what neural substrates are involved in the same.

Another aspect of decision-making that is of interest is how humans make decisions involving stimuli with social content. For example, stimuli that are evocative of animate agents akin to living things, are known to activate brain regions involved in social cognition. However, more work is needed to understand the neural substrates that are involved in decision-making about animate agents, including people. We plan to conduct behavioral and fMRI experiments to explore this topic.

Further, a core evolutionary component of the decision process is making predictions about the outcomes in order to maximize rewards and minimize threats, and make optimized decisions. Reinforcement learning is one such process where an aspect of behavior is strengthened by the delivery of a valued stimulus immediately after the occurrence of that behavior. In a series of experiments designed to probe this process, we will manipulate different components of the decision, such as number and value of response options, to understand the process and neural correlates of reinforcement learning.

C. Emotion processing

The processing of emotional stimuli in general, and emotional faces in particular, has high evolutionary and social relevance. There is mounting evidence that the amygdala is significantly involved in emotion processing and it has been shown to respond well to fearful expressions (Murphy, Nimmo-Smith, & Lawrence, 2003). We have previously shown that the amygdala responds differentially to emotional faces only when sufficient attentional resources are available

to bias processing of those faces (Pessoa et al., 2002b). We have some evidence that the top-down attentional control system (dorsomedial, lateral frontal and parietal cortices) mediates this response to or away from the emotional features. We plan to further test this by examining whether increasing task-related attentional demands (by making the top-down components of a task more difficult) elicits greater activity within systems mediating top-down attentional control and, consequently, less activity within the amygdala to the emotional expression.

In addition to being involved in fear processing (Murphy, et al., 2003), the amygdala also responds to other environmental threats (e.g., sharks) and even appetitive stimuli (Dolcos, et al., 2004). It is likely, that this response, like the response to emotional expressions (Pessoa et al., 2002) can be altered by changes in task load and the recruitment of top-down attentional control systems. To test this we will examine whether increasing task-related attentional demands will elicit greater activity within systems mediating top-down attentional control and, consequently, less activity within the amygdala to these stimuli.

Although, it does not appear that emotional faces are a “privileged” category of objects immune to top-down attentional modulation (Pessoa et al., 2002), emotional stimuli can capture attention and can interfere with on-going behavior (Mitchell, Richell, Leonard, & Blair, 2006). In addition to emotional expressions, we will extend these studies to other stimuli such as environmental threats and appetitive stimuli. Another area of interest, is what impact task-irrelevant emotional distracters might have on recruitment of top-down attentional control in processing task relevant non-emotional stimuli. In another study, we will also use stimuli from the International Affective Picture System (IAPS) to elucidate patterns of neural response to threat and illness in the entire brain.

Although the existence of a subcortical route to the amygdala has not been delineated in primates, the view is now emerging that there is a rapid amygdala response to emotional stimuli mediated by a sub-cortical visual route as well as a slower amygdala response that is mediated cortically (Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997). We have in the past used behavior and fMRI to study the role of attention and awareness in emotion processing (Pessoa et al., 2005, Pessoa et al., 2006). However, fMRI does not allow a distinction between fast and slow responding because the BOLD response is too slow. In contrast, using magnetoencephalography (MEG), a brain-imaging technique with superb temporal resolution and fairly good spatial resolution, it is possible to determine the spatiotemporal development of facial threat processing in the gamma frequency band. Using MEG we plan to test whether fearful expressions elicit an early response within the amygdala as well as a later response, following processing of the stimulus within visual cortex.

Numerous studies have shown that facial expressions can modulate brain activity, not just in the amygdala, but a whole network of cortical regions including occipital and temporal cortices. For example, angry and fearful faces evoke stronger fMRI responses than neutral faces in many brain regions including middle occipital gyrus (MOG) fusiform gyrus (FG) and superior temporal sulcus (STS). And yet, despite the fact that we can discriminate at least seven categories of expressions, there is no evidence that such differences are present in the magnitude of fMRI response. Multi-voxel pattern analysis (MVPA) is a popular analytical technique used to identify patterns of activity in different brain regions and make inferences about the involvement of those regions. We will therefore explore whether MVPA can be used to decode facial expression in human cortex.

Lastly, stimuli that signal threat show considerable variability in the extent to which they enhance behavior and neural processing, but the link between behavioral and neural variability

has not been clearly elucidated. Through behavioral and fMRI studies, we plan to link variability in behavior and personality traits with neural activation, thereby identifying neural substrates that are involved in mediating inter-subject differences in threat processing.

D. Perception

A key framework that has guided visual neuroscience is the division of cortical visual processing into distinct ventral and dorsal pathways (Ungerleider and Mishkin, 1982; Mishkin et al., 1983). Both pathways originate in V1, with the ventral pathway coursing through occipitotemporal cortex into the temporal lobe and the dorsal pathway coursing through occipitoparietal cortex into the posterior parietal cortex. Lesions of the ventral pathway in monkey produce selective deficits in object discrimination, leading to its characterization as a “What” pathway. Conversely, lesions of the dorsal pathway produce selective deficits in visuospatial tasks, leading to its characterization as a “Where” pathway. Further, the dorsal and ventral pathways extend into dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, respectively (Macko et al., 1982).

The ventral pathway in non-human primates is characterized by neurons that are selectively responsive to complex visual stimuli with visual receptive fields that increase in size along the pathway (Kobatake and Tanaka, 1994; Rousselet et al., 2004; Rust and Dicarlo, 2010). These properties are consistent with a processing pathway that is involved in object recognition, producing specific representations of objects or object features that are abstracted away from the spatial structure of the input at the retina (DiCarlo and Cox, 2007). In human fMRI, one of the most striking observations has been the presence of category-selective regions, responding selectively for particular categories, including faces (Puce et al., 1996; Kanwisher et al., 1997), objects (Malach et al., 1995; Kourtzi and Kanwisher, 2000), body parts (Downing et al., 2001; Peelen and Downing, 2007), scenes (Epstein and Kanwisher, 1998) and letter strings (Puce et al., 1996; Cohen and Dehaene, 2004; Baker et al., 2007) (Figure 4.15). Similar fMRI studies in monkeys have also revealed corresponding category-selective regions (Tsao et al., 2003; Pinsk et al., 2005; Tsao et al., 2006; Bell et al., 2009; Pinsk et al., 2009).

While the ventral pathway is characterized by its selectivity for stimulus form, the prominent feature of the dorsal pathway is selectivity for the spatial position of stimuli and, in particular, the direction of visual motion. Further, regions within the dorsal pathway seem to play a particular role in the planning and execution of limb (for reviews, see Culham and Valyear, 2006; Milner and Goodale, 2006) and eye (e.g. Konen and Kastner, 2008a) movements and posterior parietal cortex has been implicated in many aspects of attention (e.g. Shomstein and Behrmann, 2006; Medina et al., 2009) and other high-level cognitive functions (Culham and Kanwisher, 2001; Gottlieb and Snyder, 2010). Recently, it has been proposed that “Where” nor “How” are sufficient to adequately capture the diversity of visuospatial functions supported by this pathway and that instead the dorsal pathway should be viewed as a neural nexus of visuospatial processing giving rise to at least three distinct pathways: parieto-prefrontal, parieto-premotor, and parieto-medial temporal, which primarily support spatial working memory, visually guided action, and spatial navigation, respectively (Kravitz et al., 2011). Despite this characterization of the dorsal and ventral pathways as reflecting the separate processing of spatial and object properties, respectively, this separation is far from complete. Selectivity for visual form has been reported in both monkeys and humans along the dorsal pathway (Sereno and Maunsell, 1998; Konen and Kastner, 2008b), and selectivity for position is present throughout the ventral pathway (Schwarzlose et al., 2008; Kravitz et al., 2010; Cichy et al., 2011).

The major focus on the work under this theme is to further characterize and understand the organization of visual processing along these large-scale processing pathways, elucidate the nature of the representations within the different regions and investigate how object and spatial representations differ between the ventral and dorsal pathways.

The auditory system is another primary perceptual system that participates in the perception and interpretation of sounds with different degrees of complexity such as simple tones and speech. Auditory information from the cochlea arrives first to the primary auditory cortex, where basic temporal and spectral analysis of the signal takes place. From there, information flows to belt auditory regions in the superior temporal cortex, and from these regions information then flows into additional multi-modal higher order cortex distributed across the brain. Despite its importance, the functional organization of human auditory cortex has not yet been characterized beyond a rudimentary level of detail. As part of this protocol, we plan to advance our understanding of the organization of auditory cortex. In particular, we plan to take advantage of recent improvements in spatial and temporal resolution in fMRI to try to understand this system with a new level of detail.

E. Plasticity and Priming

Prior experience modulates the responses observed throughout cortical regions. Such experience might involve as little as a single presentation of a given stimulus or extensive training over multiple days or even years on discrimination and recognition of particular types of stimuli.

One of the most robust experience-related effects is the reduction of neural activity with repetition (Grill-Spector et al., 2006). Such repetition-related reduction has been observed at multiple scales in both monkeys and humans and also occurs over multiple temporal scales from milliseconds to days (e.g. Li et al., 1993; Miller and Desimone, 1994; Sobotka and Ringo, 1996; Henson et al., 2000; van Turennout et al., 2000).

Short-term training also produces modulations in the neural responses to visual stimuli. For example, human and non-human primate subjects have been trained on visual texture discrimination tasks (Karni and Sagi, 1991, 1993) or discrimination (Op de Beeck et al., 2006), individuation (Gauthier et al., 1999; Wong et al., 2009) or categorization (Baker et al., 2002; Wong et al., 2009) of novel objects. In such tasks, learning typically improves over a period of days and studies have reported both increases and decreases in response magnitude in regions activated by the stimuli, in addition to increases in selectivity.

The problem with short-term laboratory training studies is that the length of experience may not be sufficient to elicit large training effects and the type of experience may not accurately reflect the typical experience people receive. An alternative approach is to take advantage of long-term natural experience. For example, representations in body-selective cortical regions are strongest for commonly experienced configurations. Similarly, a comparison of selectivity for Hebrew words in Hebrew compared with non-Hebrew readers (Baker et al., 2007) revealed much stronger selectivity for Hebrew words in the Hebrew readers in the so-called Visual Word Form Area (VWFA). Finally, experiments with car and bird experts (Gauthier et al., 2000; Harel et al., 2010) have revealed stronger activation for objects of expertise in experts compared with novices, although such increased activation may reflect increased engagement.

The major focus on the work under this theme is to further characterize and understand how prior experiences changes the underlying neural representations throughout the cortex.

F. Moral and Social Cognition

Social cognition involves the processing of information relating to conspecifics in the brain. There have been suggestions that social cognition is mediated by a single form of mechanism. Thus, Preston and de Waal (2002) have argued that social cognition is “a super-ordinate category that includes all sub-classes of phenomena that share the same mechanism. This includes emotional contagion, sympathy, cognitive empathy, helping behavior, etc.” (p. 4; Preston & de Waal, 2002). Alternatively, it has been argued that there are computational differences between different aspects of social cognition. For example, distinctions have been drawn (Blair, 2006) between: (i) motor empathy (the tendency to automatically mimic and synchronize facial expressions, vocalizations, postures, and movements with those of another person; Hatfield, Cacioppo, & Rapson, 1994); (ii) perspective taking (i.e., Theory of Mind - the ability to represent the mental states of others [their thoughts, desires, beliefs, intentions and knowledge]; Frith, 1989); and (iii) emotional empathy (the emotional responses to emotional social [emotional expressions] cues of others; see also Section C: Emotional processing). Our work will help determine the degree of functional independence of different aspects of social cognition.

An aspect of social cognition that is of particular interest is moral reasoning. Understanding the neural systems mediating moral reasoning is important because the impairment in moral reasoning is a central component of the clinical condition psychopathy (Blair, 1995). Mirroring the situation with respect to social cognition more generally, some have suggested that the processing of all social norms is mediated by a unitary system (Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005). Alternatively, it has been argued that there are distinct differences in the systems mediating care-based norms (concerning actions that harm others), disgust based norms (concerning actions which initiate disgust reactions in those disapproving of them) and authority based norms (concerning actions focused around social hierarchy); (Blair, 2007; Schnall, Haidt, Clore, & Jordan, 2008). It is argued that these different norms are acquired through different forms of emotional learning mediated by different neural systems (Blair, 2007). Our work focuses on two aspects of moral reasoning: (i) identifying the regions involved in processing different forms of social norm; (ii) understanding the functional roles of these systems in moral reasoning (e.g., if ventromedial frontal cortex is involved in the representation of reinforcement value will its role in moral reasoning reflect the reinforcement value of the action being processed?).

G. Methods Development and Evaluation

Fundamental to quality fMRI research in the field of psychology and neuroscience, is a focus on maintaining a high level of sophistication with regard to imaging methods and hardware, processing methods, paradigm development, and interpretation of the fMRI signal. Methods development is an integral part of our lab's work, since cutting edge methods are tightly integrated with the other projects in this protocol. Our efforts on this front include several topics.

First, we plan to conduct studies aimed at the development of multivariate analysis approaches to fMRI data. More and more fMRI applications are starting to move away from simple univariate, group-averaged data. The multivariate analysis method development considers all voxels as contributing in a unique manner to the signal, resulting in an increase in power and ability to assess neural activation patterns in individual subject data.

Second, we will develop and assess new arterial spin labeling (ASL) techniques for fMRI studies. ASL is a more direct, stable, and quantitative measure of brain activity and also provides a baseline perfusion map, but suffers from lower temporal resolution and far less

sensitivity than standard BOLD fMRI techniques. We will conduct experiments that will help to improve the utility of ASL as well as pilot projects that might lend themselves well to ASL approaches.

Third, we plan to perform a systematic quantitative calibration of the fMRI signal. For group-level analyses of fMRI, it is desirable to have better BOLD estimates. It is also important to accurately determine and map all variables that contribute to BOLD on a voxel-wise basis. Global physiologic stressors such as breath holding and breathing CO₂ are useful calibrating modulations in that they cause global changes in many of the variables but do not cause brain activation. We plan to actively develop these techniques, so as to make them easier to implement and more powerful.

Further, we plan to develop and evaluate real time fMRI (rt-fMRI) methods. The ability to receive functional maps in real time lends itself well to certain types of experiments in which data are fed back to the subject or in which data quality and maps are required to enable decisions on what types of stimuli to present from moment to moment. rt-fMRI is technically demanding, and we plan to use a cross-disciplinary approach to optimize its development and application.

Another goal under this theme is to better understand the BOLD signal on an individual subject basis. For this we will use experiments with long paradigms with either synthetic or natural stimuli for improving single subject assessment of whole-brain connectivity. For this we will collect large amounts of data from single subjects over multiple visits. By applying model free or minimally constrained analyses to these data, we expect to find that the entire brain is active in different ways for most tasks, a finding that is potentially quite useful for all ongoing fMRI studies. In addition, our preliminary data indicate that resting state fMRI (rs-fMRI) data are not stable over time, since a subject's mental state may fluctuate between several "states" during a typical run. Better understanding and use of this knowledge can further enhance the information that is obtained from resting state data.

In addition to functional imaging of the brain, we plan to conduct several experiments to develop novel ways of structural imaging, such as diffusion tensor imaging (DTI) methods. On this front we plan to conduct experiments to optimize the technically demanding diffusion acquisition and processing methods, and then apply the optimized parameters to gather data to address research questions about brain connectivity.

2. Study objectives

This protocol covers experiments under several themes of cognition, and thus, for clarity, we are listing the objective of each experiment along with its rationale/background and significance of result, in this section, rather than in the Introduction. In the Procedures section we have outlined the main methods used in this entire protocol such as fMRI and MEG, and also specifics of each task as they relate to each of the primary objectives.

The objectives of this study can be broadly categorized under the following 7 themes:

A. Attention

What are the cortical regions involved in endogenous and exogenous visual attention? (Ungerleider)

Primary Objective: To investigate the involvement of cortical areas during top-down endogenous control of attention and bottom-up exogenous orienting of attention.

Background:

Previous research into visual attention in the brain has identified a top-down control system, which acts in a goal-directed, endogenous manner, and a bottom-up system that responds to unexpected stimuli in an involuntary, exogenous manner. It is well known that a dorsal fronto-parietal network of regions including frontal eye fields (FEF), supplementary eye fields (SEF) and intra-parietal sulcus (IPS) is engaged in the top-down control of visual attention (e.g. Corbetta et al., 1998; Kastner et al., 1999; Hopfinger, Buonocore, & Mangun, 2000). However not much is known about the mechanism of exogenously driven attention, and the regions that are involved in its mediation. Some researchers (Corbetta et al., 2008) have proposed that regions such as temporoparietal junction (TPJ) and middle frontal gyrus (MFG) may be involved in the propagation of bottom-up sensory driven exogenous attention. We therefore wish to test this hypothesis by using fMRI to look at brain activity while subjects perform a task that engages endogenous or exogenous attention. Specifically we plan to test the involvement of regions such as TPJ and middle and inferior frontal cortices in propagating information about a salient cue that precedes a task-relevant stimulus. We plan to contrast the involvement of these regions with those involved in top-down endogenous attention such as IPS, FEF and SEF.

Significance:

Results from these experiments will help to pinpoint the neural circuitry underlying the facilitation that is seen in stimulus processing when stimuli are exogenously cued. This will help to better understand and differentiate mechanisms of visual attention.

Spatial selectivity in the exogenous attention system (Ungerleider)

Primary objective: To detect the hypothetical spatial selectivity of exogenous attention, we will use multi-voxel pattern analysis (MVPA) on fMRI data acquired while fixating subjects passively view brief, infrequently presented stimuli at various spatial locations. Unlike traditional analysis methods, MVPA can detect fMRI selectivity even when the functional anatomy is overlapping and distributed.

Background:

Endogenous attention is attention that is goal-directed and voluntary. Many cortical regions implicated in endogenous attention are spatially selective (Silver et al. 2005; Hansen et al. 2007; Silver & Kastner, 2009). That is, the overall pattern of activity depends on a spatial factor such as the location of covert attention or the destination of a saccade. These experimental demonstrations imply that the underlying neural populations have access to information about spatial location. Hypothetically, spatial information might allow a neural population to focus available computing resources on stimuli in the relevant parts of visual space. It is reasonable to assume that access to spatial information would also be adaptive for regions implicated in exogenous attention - attention that is stimulus-driven and involuntary (Arrington et al., 2000; Downar et al., 2000; Corbetta & Shulman, 2002; Macaluso et al., 2002; Shulman et al., 2010; Dodds et al., 2011). Therefore, it is striking that spatial selectivity has not previously been demonstrated in such regions as the TPJ and inferior parietal lobule (IPL), which are known to respond robustly to stimuli that elicit exogenous attention. We hypothesize that previous efforts to reveal spatial selectivity in these regions (Serences, 2005; Corbetta & Shulman, 2002) failed not because there is no spatial selectivity, but because the cortical locations selective for different parts of space are overlapping and distributed.

Significance:

A demonstration of spatial selectivity in such regions as the TPJ and IPL, which are known to respond robustly to stimuli that elicit exogenous attention, will not only be novel, but will be relevant to the clinical literature. ROIs emerging from studies manipulating exogenous attention typically overlap with regions where lesions often lead to persistent and severe spatial neglect. Spatial neglect is the failure to report, respond, or orient to novel or meaningful stimuli presented to the side of space opposite a brain lesion, when this failure cannot be attributed to either elemental sensory or motor defects. Typically, persistent and severe neglect is caused by damage to the right hemisphere. One neuroanatomical model of spatial neglect (Kinsbourne, 1977; Kinsbourne, 1993) proposes that the disorder arises because spatial representation in the damaged brain regions is contralateral in the left hemisphere and both contralateral and ipsilateral in the right hemisphere. Another model (Corbetta and Shulman, 2011) proposes that hemispheric asymmetry occurs in spatial neglect not because of an asymmetry in spatial attention per se, but because the exogenous attention system is right lateralized and interconnected with a bilateral endogenous attention system that represents space contralaterally. Any characterization of spatial selectivity patterns in the exogenous attention network is likely to contradict one or both of these competing models.

What is the role of attention in perceptual learning? (Ungerleider)

Primary Objective: To understand the underlying neural mechanisms of perceptual learning facilitated by exogenous attention we will examine the dynamic changes in brain activations in early visual areas by using fMRI. The experimental paradigm used in Mukai et al., (2011) allows us to use a within-subjects comparison of changes in brain activations in early visual areas in response to the trained stimulus with or without exogenous attention.

Background:

Attention has been implicated in psychophysical, electrophysiological and human fMRI studies as playing a key role in explaining the variability in perceptual learning among subjects (Shiu & Pashler, 1992; Ahissar & Hochstein, 1993; Crist et al., 2001; Li et al., 2004; Fahle, 2004, Mukai et al., 2007). However, another line of evidence indicates that attention does not play an important role in perceptual learning (Watanabe et al., 2001; Watanabe et al., 2002; Seitz & Watanabe, 2003; Nishina et al., 2007). Our previous psychophysical study (Mukai et al., 2011) examined the role of attention in perceptual learning and found contrast sensitivity improvement at locations trained with exogenous attention but not with endogenous attention.

Significance:

The findings of how the changes in brain activations occurs to learned stimuli will give us valuable insight into the underlying neural mechanisms of perceptual learning facilitated by exogenous attention.

How do covertly observed fluctuations in sustained attention – and neurofeedback of these fluctuations – map from brain to behavior? (Bandettini)

Primary Objective: To observe and modulate subjects' level of mind-wandering by developing a covert, real-time measure of attention to the task at hand.

Background:

People spend approximately 47% of their waking hours thinking about something other than the task at hand (Killingsworth & Gilbert, 2010). This propensity for mind-wandering can have detrimental effects in situations where sustained attention is critical for success, such as listening to a lecture in the classroom (Szpunar et al., 2013). However, current methods for observing mind-wandering generally require overt assessments that stop the mind-wandering process

(Smallwood & Schooler, 2006). That is, current methods are unable to recognize fluctuations in sustained attention as it ebbs and flows unimpeded.

Significance:

The findings from this experiment may shed light on the task-independent indicators of sustained attention and the time-course of mind-wandering. This will have implications and potential applications for a variety of individuals for whom sustained attention is critical for success, including students in the classroom, security and manufacturing personnel, and members of the military.

B. Decision-making

What are the brain regions whose activity predicts individual differences in the use of prior knowledge during decision-making? (Ungerleider)

Primary objective: It is known that the degree to which decision bias in prior knowledge tasks approximates optimality varies widely across individuals. Here, we will seek to exploit that variability to locate the brain areas in which activity changes correlate with the extent of the bias shift.

Background:

When making decisions, people take advantage of available prior knowledge to help them make choices. For example, consider a prior knowledge condition indicating that Alternative 1 has an 80% and Alternative 2 has a 20% chance of being the correct choice – we will call this an 80/20 prior knowledge condition – and a 50/50 prior knowledge condition indicating that Alternatives 1 and 2 each have a 50% chance of being the correct choice. Unsurprisingly, human subjects tend to choose Alternative 1 more often when the prior knowledge condition is 80/20 than when it is 50/50 (Green & Swets, 1966; Healy & Kubovy, 1978; Healy & Kubovy, 1981); we refer to this common-sense behavior as biasing decisions in favor of Alternative 1. Despite the usefulness of this decision-making strategy, it is not clear which brain regions subserve this behavior.

Significance:

Previous brain imaging studies in our laboratory have implicated certain brain regions in the use of prior knowledge to bias decisions (Hansen, Hillenbrand, & Ungerleider, 2011). However, the previous work analyzed differences across trial type defined by target only. Performing a whole-brain search for regions where activity changes correlate with behavior changes across subjects as in this case is a more direct way to locate the brain areas subserving the adaptive use of prior knowledge in decision-making.

Perception vs. judgment: Are there stimulus specific effects of prior knowledge on decision-making? (Ungerleider)

Primary objective: To identify brain regions with differential activation for perceptual vs. categorical uncertainty during decisions made under prior knowledge. We will control for stimulus-level confounds by testing whether differences found are also present in a control sample of subjects who have not been exposed to the prior knowledge condition.

Background:

Humans use prior knowledge to bias decisions made under uncertainty. However, not all uncertainty conditions are alike. In the laboratory, one common manipulation in perceptual decision studies is to degrade targets with noise (perceptual uncertainty), while another is to present targets in two overlapping categories such that intermediate targets are ambiguous (categorical uncertainty). Behaviorally, when prior knowledge indicates that one alternative is

likelier than another, human subjects bias their decisions in favor of the indicated alternative in both uncertainty conditions (Green and Swets, 1966). In this fMRI study we predict that when prior knowledge is added to decisions made under perceptual vs. categorical uncertainty, the behavioral bias shift is subserved by different brain mechanisms.

Significance

Showing that different types of uncertainty elicit prior knowledge related activity in different parts of the brain will demonstrate that there is not a single “prior knowledge area” that combines prior knowledge with stimulus information in all decision paradigms. This finding will contradict the simplest biological version of the standard signal detection / diffusion model of decision-making (Gold & Shadlen, 2007; Ratcliff & McKoons, 2008), showing that this model is not literally instantiated in the brain.

What is the role of reward in perceptual decision-making? (Ungerleider)

Primary Objective: To investigate how incentive in the form of a monetary reward influences decision-making and what neural substrates mediate this effect.

Background:

Studies suggest that higher-level cortical areas may compute perceptual decisions by comparing outputs of different pools of selectively tuned lower-level sensory neurons. A factor that may influence this decision-making process is the reward value associated with making a particular response choice. Indeed, the goal of a decision maker is to maximize the expected value (Green and Swets, 1966). Our aim with this project is to specifically ask the question: *how does the introduction of an incentive such as a monetary reward affect the decision-making process?* A rich animal literature (Hikosaka et al., 1989; Apicella et al., 1991; Robbins and Everitt, 1996; Kawagoe et al., 1998; Hassani et al., 2001; Cromwell and Schultz, 2003; Voorn et al., 2004) and recent human neuroimaging studies (Breiter et al., 1997; Koepp et al., 1998; Delgado et al., 2004; Knutson and Cooper, 2005; Heekeren et al., 2007) have implicated the striatum in aspects of reward processing such as reward value, reward anticipation, reward prediction, etc. We therefore hypothesize that striatal regions will be activated during perceptual decision-making, and provide information related to the incentive/reward to decision-making areas, such as the DLPFC. Further, activity in visual processing areas should correlate with the magnitude of reward, presumably due to information about reward value being fed back to these areas.

Significance:

We expect that incentive (in the form of a monetary reward) will influence decision-making by biasing subjects towards the more profitable choice (shift in decision criterion). Subjects will also be quicker to make this biased choice compared to the less profitable option. No change in sensitivity, as measured by d' , is expected. We will analyze fMRI data to: 1) determine whether the dorsal striatum encodes the reward value, by looking at the fMRI activity in that region during the cue period; 2) probe brain regions to which the dorsal striatum propagates reward value information, by identifying areas whose activity correlates highly with that of a seed voxel in the dorsal striatum; 3) examine how the DLPFC incorporates sensory evidence and reward value to arrive at a decision, by correlating activity in DLPFC with a mathematical combination of activity in face-selective, house-selective and reward-related areas (similar to Heekeren et al., 2004); and 4) define which regions are involved in error monitoring, by contrasting activity during the feedback period on incorrect vs. correct trials.

How do simultaneous changes in perceptual and reward uncertainty impact neural dynamics and decision-making? (Ungerleider)

Primary Objective: To investigate the behavioral and associated neural dynamics that mediate decision-making when both visual sensory information and reward outcomes are uncertain.

Background:

In complex real-world environments, individuals must determine, simultaneously, what stimuli are (perceptual decision-making) and what they are worth (reward-based decision-making). While traditionally these are theoretically and computationally separate sub-domains of research, recent evidence suggests that decision-making behavior is best modeled through a combination of sensory and reward information, rather than either alone (Navalpakkam, Koch, Rangel, & Perona, 2010; Towal, Mormann, & Koch, 2013). Additionally, a number of clinical conditions such as Autism Spectrum Disorders (Chiu et al., 2008; Dakin & Frith, 2005; Robertson, Martin, Baker, & Baron-Cohen, 2012) and Schizophrenia (Cavallaro et al., 2003; Chau, Roth, & Green, 2004) are impacted by atypicalities in *both* perceptual and reward-based decision-making domains. In healthy participants, findings suggest an interaction between perceptual and reward information that guides which choices are made and how decisions are reached. For example, altering the reward value associated with uncertain sensory information decreases the amount of sensory information necessary to reach an accurate decision (Summerfield & Koechlin, 2010). Similarly, changing the degree of sensory noise present in a stimulus can bias choices towards less rewarded, but more perceptually salient, options (Lou, Hsu, & Sajda, 2015). However, it is unclear whether these biases and sensory-outcome interactions are the product of changes in a single domain-general decision network, or reflective of the dynamics between domain specific “perceptual” and “reward-based” decision systems. The purpose of the proposed study is to elucidate the behavioral and associated neural substrates of simultaneous manipulations of perceptual and reward information using fMRI. Very recently, methods have been developed that allow perceptual and reward-based decision-making behavior to be modeled through shared computational approaches, such as sequential sampling models and Bayesian predictive coding models. This opens doors to the comparable study of the interactions between them, and the ability to uncover their distinct and shared neural substrates.

Significance:

The findings of this study will be important in understanding normative decision-making processes across the sub-domains of perceptual- and reward-related processes in decision making, and may provide insight into how alterations in neurobiology can lead to individual differences in choice behavior with future extensions to clinical samples.

Effects of perceived animacy on neural mechanisms of decision-making (Martin)

Primary objective: To determine how perceived animacy influences neural mechanisms of decision-making.

Background:

It has been well established that simple visual stimuli whose motion is evocative of animate agents (i.e., living things that move on their own) or which appear in contexts associated with animate agents activate brain regions important for social cognition. However, the influences of perceived animacy on regions important for aspects of cognition, including decision-making, are not understood. Such work is needed because a lifetime of social experiences may influence the development of neural substrate involved in making decisions about animate agents, including people. However, it is difficult to distinguish regional activation associated with different

components of decision-making, and influences of animacy on those mechanisms, with standard fMRI designs.

Significance:

The proposed research is expected to give a detailed understanding of how animacy influences the neural mechanisms of decision-making at the regional and circuit level.

Do humans learn category assignments more quickly in asymmetrical reinforcement conditions? (Leopold)

Primary Objective: To investigate how symmetrical and asymmetrical reinforcement conditions influence learning on a categorization task.

Background:

Experiments in laboratory animals have identified differences in the efficacy of symmetrical versus asymmetrical reinforcement in categorization tasks. When there are two categories of objects, monkeys learn more rapidly with asymmetrical reinforcement (where one category is associated with a positive outcome and another with a negative outcome) than with symmetrical reinforcement (where distinct responses to the two categories are each positively reinforced). This difference is thought to reflect the recruitment of different neural mechanisms in the two reinforcement conditions.

We have recently devised an asymmetrical reinforcement method that allows monkeys to correctly assign dozens of arbitrary visual stimuli into two artificial categories during less than an hour of training, which is much faster than would be expected using symmetrical reinforcement. We propose to test whether human subjects show a similar difference in the rate learning based on the symmetry of response reinforcement.

Significance:

Results from this study will shed light on the process of response reinforcement and will help guide future studies on reinforcement learning during decision-making.

What is the role of the ventromedial prefrontal cortex (VMPFC) in encoding expected reinforcement outcomes during decision-making? (Blair)

Primary Objective: To determine whether VMPFC is involved in the representation of expected reinforcement outcomes during decision-making.

Background:

Passive avoidance learning involves responding to “good” stimuli that engender reward (point gain) and withholding responses to “bad” stimuli that engender punishment (point loss). Successful passive avoidance learning is thought to involve the stimulus-reinforcement associations to guide decision-making (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000). Relatively little is known about this process though ventromedial frontal cortex (VMPFC) is thought to be involved. However, understanding this process is important. A failure to use stimulus-reinforcement associations generally and poor performance on the passive avoidance learning task were one of the earliest identified markers of psychopathic traits (J.P. Newman & Kosson, 1986). The current study tests whether VMPFC is involved in the representation of expected reinforcement outcomes during decision-making.

Significance:

Results from these experiments will determine whether VMPFC is involved in the representation of expected reinforcement outcomes during passive avoidance learning. This information is important as VMPFC is thought to be disrupted in individuals with psychopathy

and failure to perform the passive avoidance task is a marker for this disorder. Thus, these data will help us understand this disorder.

The selection of response options on the basis of reinforcement expectancies: the impact of inter-object reinforcement distance (Blair)

Primary Objective: To determine the functional contributions of VMPFC and DMPFC in decision-making.

Background:

Ventromedial frontal cortex (VMPFC) and dorsomedial frontal cortex (DMPFC) are both implicated in decision-making. However, their specific functional contributions remain unclear (Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Specifically, it is unclear whether, both these brain regions, or only VMPFC, represent the reinforcement levels associated with respected choices. Moreover, it is unclear whether decision difficulty influences activity in both regions or only within DMPFC. Decision difficulty can be manipulated by altering the inter-object reinforcement distance – the difference in the values between the options to be chosen between. The current study is intended to distinguish between these hypotheses by examining the impact of reinforcement value and inter-object reinforcement distance on activity within VMPFC and DMPFC.

Significance:

Results from these experiments will help to identify the functional roles of the neural systems involved in decision-making. Decision-making difficulties are central to many mood and anxiety disorders. Specifically, these data will have direct relevance to understanding the decision-making difficulties faced by individuals with psychopathy.

The selection of response options on the basis of reinforcement expectancies: the impact of number of response options (Blair)

Primary Objective: To determine the functional contributions of VMPFC and DMPFC in decision-making.

Background:

Ventromedial frontal cortex (VMPFC) and dorsomedial frontal cortex (DMPFC) are both implicated in decision-making. However, their specific functional contributions remain unclear (Rushworth, et al., 2011). Specifically, it is unclear whether both or only VMPFC represents the reinforcement levels associated with respect choices. Moreover, it is unclear whether decision difficulty influences activity in both or only within DMPFC. Decision difficulty can be altered by altering the number of response options (choosing between two objects is easier and RTs are faster, than when choosing between four objects). The current study is intended to distinguish between these hypotheses by examining the impact of reinforcement value and number of response options on activity within VMPFC and DMPFC.

Significance:

Results from these experiments will help to identify the functional roles of the neural systems involved in decision-making. Decision-making difficulties are central to many mood and anxiety disorders. Specifically, these data will have direct relevance to understanding the decision-making difficulties faced by individuals with psychopathy.

What are the functional roles of ventromedial, dorsomedial and inferior frontal cortices during reversal learning? (Blair)

Primary Objective: To determine the functional contributions of VMPFC, DMPFC and IFC in reversal learning.

Background:

Ventromedial frontal cortex (VMPFC), dorsomedial frontal cortex (DMPFC) and inferior frontal cortex (IFC) have all been implicated in reversal learning. However, their specific functional contributions remain unclear (Rushworth, et al., 2011). Specifically, it is unclear whether VMPFC is only sensitive to changes in outcome information and whether DMPFC and IFC only respond when it is necessary to over-rule a prepotent response or alternatively whenever an error is made.

Significance:

Results from these experiments will help to identify the functional roles of the neural systems involved in reversal learning. Reversal learning difficulties are seen in psychopathy (Budhani, Richell, & Blair, 2006). As such these data will have direct relevance to understanding the reversal learning deficits seen in psychopathy.

What is the functional role of ventromedial frontal cortex during operant extinction? (Blair)

Primary Objective: To determine the functional contributions of VMPFC during operant extinction in humans.

Background:

Operant extinction, which features modification of instrumental responses to stimuli following a change in associated reinforcement, is an important form of learning for dynamic environments. Impaired operant extinction is a marker for psychopathy (J.P. Newman, Patterson, & Kosson, 1987). As such understanding the neural systems involved in operant extinction is important. Animal work suggests that ventromedial prefrontal cortex (VMPFC) plays an important role (Schoenbaum, Setlow, Saddoris, & Gallagher, 2005). However, no work has examined the issue in humans.

Significance:

Results from these experiments will help to identify the functional roles of VMPFC in operant extinction. Operant extinction is a marker for psychopathy (J.P. Newman, et al., 1987). As such these data will have direct relevance to understanding the disorder of psychopathy.

What is the neural basis of the optimistic bias? (Blair)

Primary Objective: To determine neural regions implicated in assessing the probability of negative and/or positive events occurring to the self in the future.

Background:

Optimistic bias is the tendency to believe that negative events are less likely, and positive events more likely, to happen to oneself than to others (Weinstein, 1980). It can lead to serious underestimations of health and economic risks. As such an understanding of the neuro-cognitive systems mediating optimistic bias is important. However, only one previous study has investigated the issue (Sharot, Riccardi, Raio, & Phelps, 2007). This study implicated ventromedial prefrontal cortex (VMPFC), a region critical for decision-making. However, design limitations make the interpretation of this previous study difficult. We therefore wish to determine whether VMPFC is critically involved in assessing the probability of positive events.

Significance:

Results from these experiments will help to identify the neural regions mediating the optimistic bias. Such data has implications for understanding the risk assessments of healthy participants and for understanding why this bias can be absent, or significantly reduced, in some patient populations.

C. Emotion processing

Uncovering variability in fearful face processing in healthy individuals using prior probability (Ungerleider)

Primary Objective: To determine the neural substrates underlying variability in fear processing and personality traits.

Background:

While the research community agrees that threat has a privileged status in the brain, this status is not fixed and can vary even among healthy individuals. Previous work has implicated anxiety levels as a major source of this variance in how healthy individuals processing threat, but all work to date has pre-selected those healthy subjects with the highest and lowest anxiety levels (Mogg and Bradley, 1999; Richards et al., 2002; Surcinelli et al., 2006; Winton et al., 1995). This experiment will focus on categorizing the natural spectrum of behavior for detection of fearful faces and using this variance to guide neural and personality analyses.

Significance:

We expect that results from this work will challenge the previously held view that all healthy individuals should show behavioral and neural enhancements for threatening stimuli like fearful faces. It additionally underscores the importance of viewing healthy subjects as a heterogeneous population rather than assuming homogeneity in threat processing for all healthy individuals.

Facial expression and identity processing investigated using multi-voxel pattern analysis methods (MVPA) (Ungerleider)

Primary Objective: Does there exist a local brain region or an independent distributed network for facial expressions discrimination and classification? Can different facial expressions be decoded from the patterns of neutral activity measured with fMRI?

Background:

Numerous studies have show that facial expressions can modulate brain activity, as measured by fMRI. For example, angry and fearful faces evoke a stronger fMRI response than neutral faces. And yet, despite the fact that we can discriminate at least 7 categories of expressions, there is no evidence that such differences are present in magnitude of fMRI response. In this study, we will explore whether MVPA can be used to decode facial expressions and identity in human cortex. Further we will explore whether similar or different regions encode identify vs. expression.

Significance:

Results from this work will allow us to understand how facial expressions and identity are represented in the brain. Also, we expect to clarify the roles of the amygdala, superior temporal sulcus, fusiform face area, as well as parts of inferior temporal cortex in facial expression and identity classification/discrimination.

The temporal dynamics of the response to fearful expressions (Blair)

Primary Objective: To determine whether fearful expressions elicit an early response within the amygdala (<80ms,) as well as a later response (>180ms), following processing of the stimulus within visual cortex.

Background:

It has been argued that there is a rapid amygdala response to emotional stimuli mediated by a sub-cortical visual route as well as a slower amygdala response that is mediated cortically (Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997). However, fMRI does not allow a distinction between fast and slow responding because the BOLD response is too slow. In

contrast, using magnetoencephalography (MEG), a brain-imaging technique with superb temporal resolution and fairly good spatial resolution, it is possible to determine the spatiotemporal development of facial threat processing in the gamma frequency band. The current study tests whether fearful expressions elicit an early response within the amygdala as well as a later response, following processing of the stimulus within visual cortex.

Significance:

Results from this experiment will determine whether there is an early as well as a late response within the amygdala to fearful expressions. Understanding the spatiotemporal development of fearful expression processing is important as many mood and anxiety disorders are associated with dysfunction in the processing of fearful facial affect. In particular, individuals with psychopathy show profound impairment in the recognition of fearful facial expressions (Marsh & Blair, 2008).

The impact of processing load on the response to emotional expressions (Blair)

Primary Objective: To determine whether dorsomedial, lateral frontal and parietal cortices show increased activity with increasing task load and whether this is accompanied by decreased amygdala responses to emotional distracters.

Background:

The amygdala shows a response to fearful expressions (Murphy, Nimmo-Smith, & Lawrence, 2003). This response can be modulated by altering the participant's attention. If this is focused on the facial features the amygdala response increases, whereas if it is focused on other features in a visual array, the amygdala response decreases (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). It can be assumed that the top-down attentional control systems (dorsomedial, lateral frontal and parietal cortices) are mediating the response to or away from the emotional features. However, this has not been tested. The current study examines whether increasing task-related attentional demands (by making the top-down components of a task more difficult) will elicit greater activity within systems mediating top-down attentional control and, consequently, less activity within the amygdala to the emotional expression.

Significance:

Results from this experiment will determine the impact of the recruitment of top-down attentional control systems on the amygdala's response to fearful expressions. This information is important as there remains debate in the literature on psychopathy regarding whether this disorder reflects a primary emotional deficit (Blair, 2007) or a secondary consequence of heightened top-down attentional control (J. P. Newman, Curtin, Bertsch, & Baskin-Sommers, 2010). By understanding the interaction of top-down attention on the emotional response in healthy individuals we can develop tests to appropriately examine this question in individuals with psychopathy.

The impact of processing load on the response to environmental threats and appetitive stimuli (Blair)

Primary Objective: To determine whether dorsomedial, lateral frontal and parietal cortices show increased activity with increasing task load and whether this is accompanied by decreased amygdala responses to environmental threats and appetitive stimuli.

Background:

The amygdala shows a response to fearful expressions (Murphy, et al., 2003) but also to other environmental threats (e.g., sharks) and even appetitive stimuli (Dolcos, LaBar, & Cabeza, 2004). Presumably, this response, like the response to emotional expressions (Pessoa, et al.,

2002) can be altered by changes in task load and the recruitment of top-down attentional control systems (dorsomedial, lateral frontal and parietal cortices). However, this has not been tested. The current study examines whether increasing task-related attentional demands (by making the top-down components of a task more difficult) will elicit greater activity within systems mediating top-down attentional control and, consequently, less activity within the amygdala to environmental threats and appetitive stimuli.

Significance:

Results from this experiment will determine the impact of the recruitment of top-down attentional control systems on the amygdala's response to environmental threats and appetitive stimuli. This information is important as there remains debate in the literature on psychopathy according to whether this disorder reflects a primary emotional deficit (Blair, 2007) or a secondary consequence of heightened top-down attentional control (J. P. Newman, et al., 2010). By understanding the interaction of top-down attention on the emotional response in healthy individuals we can develop tests to appropriately examine this question in individuals with psychopathy.

The impact of emotional distracters on the recruitment of systems involved in top-down attentional control (Blair)

Primary Objective: To determine whether the recruitment of dorsomedial, lateral frontal and parietal cortices is disrupted in the presence of threatening and appetitive emotional distracters.

Background:

The amygdala shows a response to fearful expressions (Murphy, et al., 2003) but also to other environmental threats (e.g., sharks) and even appetitive stimuli (Dolcos, et al., 2004). Emotional (amygdala) responding can be reduced by increasing top-down attention towards non emotional features of a stimulus array (Pessoa, et al., 2002). However, emotional stimuli also capture attention and can interfere with on-going behavior (Mitchell, Richell, Leonard, & Blair, 2006). As such, it appears plausible that emotional distracters might interfere with the recruitment of systems involved in top-down attentional control. However, this has not been tested.

Significance:

Results from this experiment will determine whether responding to emotional distracters can interfere with the recruitment of top-down attentional control systems. This information is important when considering mood and anxiety disorders such as Post Traumatic Stress Disorder (PTSD) where emotional information is considered to significantly interfere with on-going behavior (Vythilingam et al., 2007). By understanding the impact of emotional distracters on the recruitment of systems involved in top-down attentional control in healthy individuals, we can develop tests to appropriately examine this question in individuals with PTSD.

Neural circuits for representing threat and illness (Martin)

Primary objective: To elucidate the patterns of neural response to threat as represented by visual depictions of people, objects, and illness.

Background:

Behavioral studies have shown that viewing of threatening images can elicit release of cortisol (Codispoti et al., 2003) and viewing images of illness (coughing, sneezing) can elicit an immune response (Schaller et al., 2010). Little is known about the neural circuits that mediate these responses.

Significance:

Results from this experiment will elucidate the neural circuits that represent threat and illness in the human brain.

D. Perception

Is the contribution of the dorsal visual stream to shape perception tuned to tool-like objects or does it respond similarly to multiple object categories? (Ungerleider)

Primary Objective: To understand whether dorsal stream regions that respond to shape-change detections are engaged differently for tools compared to other objects.

Background:

Several studies have shown that, under fMRI, viewing and naming tools leads to significantly more activation within left posterior parietal cortex (Brodmann area 40: Chao & Martin, 2000; Chao et al., 1999) compared to activation observed when other object categories (such as animals or faces) are presented. The tool selective responses in left posterior parietal cortex, however, may not necessarily reflect shape processing per se, but rather information about the hand and finger movements associated with the use of the manipulable, man-made objects presented. As such, it would be interesting to explore whether dorsal stream regions that respond selectively to shape-change detections will show enhanced activation in a shape-change detection task that involves images of tools, compared to the same task when images of other object categories are used.

Significance:

By contrasting BOLD activation and MEG activity observed during shape-change detection, to activation observed in a location- or a texture-change detection task that uses the same object images (tools and non-tools), we can effectively eliminate activation in response to (i) the object images presented and (ii) any motor actions associated with them. Controlling for the above factors will allow us to infer whether shape processing within the dorsal visual stream is optimized for the perception of tool-like objects or whether it extends to multiple object categories.

Is shape processing in the dorsal visual stream comparable to shape processing in the ventral visual stream? (Ungerleider)

Primary Objective: To understand whether dorsal stream regions that respond to shape-change detections process information similarly to equivalently activated regions within the ventral stream.

Background:

In our preliminary experiments, both ventral and dorsal stream regions were equally active during shape-change detections. In addition, the ventral and dorsal activation in response to shape processing correlated with corresponding behavioral performance. Further, location-change detection was slowed down by the presence of a shape-change distracter irrelevant to the task. The above findings suggest that the dorsal visual stream may contribute to shape perception. The findings thus far, however, provide little information on the nature of the contribution of the dorsal visual stream to shape perception.

One possible hypothesis is that the contribution of the dorsal stream to shape perception arises because changes in an object's shape alter locations as well, but with respect to the object rather than to the scene. As a result, the analysis of location is intrinsic to the processing of shape, and mechanisms devoted to object locations in scenes can be recruited for the requisite processing of locations in objects. The above hypothesis can be tested in an experiment where location processing at the scene level can be contrasted with location processing internal to the object itself.

The connection between shape and location within objects is supported by theories proposing that objects are perceived as a conjunction of shape features, marked by points of

concavity on local contours and bound to specific relative locations (Biederman, 1987; Hayworth & Biederman, 2006; Op de Beeck, Torfs & Wagemans, 2008). Under this framework, some aspect of location processing is integral to the determination of shape.

Significance:

Results from this study will elucidate the nature of the contribution of the dorsal visual stream to shape perception.

Inhibition between face and house processing in the ventral stream (Ungerleider)

Primary Objective: To test for neural inhibition between the well-known visual processing pathways for face and house processing in the ventral visual stream.

Background:

It is well known that the fusiform face area (FFA) and parahippocampal place area (PPA) are activated by *different* visual stimuli (e.g. houses and faces, respectively). Preliminary tests with a wider range of visual stimuli, and with stimulus-unrelated experiments of ‘resting state functional connections’, suggest further that these two areas share mutually inhibitory neural connections. Here, we plan to test more directly if those two regions inhibit each other, using fMRI.

Significance:

Hypothetical demonstration of neural inhibition between these two areas would suggest that perception of one classification of stimuli (e.g. faces) decreases the ability to perceive the other classification (e.g. houses). If confirmed, this will comprise a novel, low level form of ‘attention’ between higher level categories.

Curvature: a crucial dimension for face processing (Ungerleider)

Primary Objective: To understand the underlying mechanisms of face processing.

Background:

We recently demonstrated in macaques that an anatomically segregated network of cortical regions is activated more by curved compared to rectilinear shapes (Yue et al., 2012 SfN). This network includes three separate regions, which partially overlap the face-selective regions. This overlap raises the question of whether curvature processing is functionally related to face processing, and whether the input to face processing originates from the curvature-processing network. Two related experiments will investigate these questions.

Significance:

The results will provide fundamental insights into how faces are extracted and processed neutrally and computationally. This knowledge will help understand deficits in social communication, a key component of autism.

How do we understand other’s actions? (Ungerleider)

Primary Objective: To understand the underlying neural mechanisms of reading human actions

Background:

When observing others’ actions, we can comprehend both the form of their movements and the goal of their actions. Watching someone reaching for a target, for example, we can determine the direction of the movement of the hand and arm. We can also identify the target as the goal of their reach. Which brain regions are involved in understanding the form and the goal of actions? Many brain regions have been suggested as the neural substrates of action understanding, including regions in human parietal, premotor, prefrontal and superior temporal cortex (e.g., Buccino et al., 2001; Grafton and Hamilton, 2007; Grossman & Blake 2002; Lestou et al., 2008). The specific role of each of these regions in action understanding, however, is still

not fully understood. Here, we will use videos of simple reaching movements to probe the role of these regions in action form and action goal understanding. Similar attempts have been made in the past (Grafton and Hamilton, 2007; Lestou et al., 2008), but those studies have either used uncontrolled stimuli (Grafton and Hamilton, 2007) or have not isolated the form and goal of actions in a controlled manner (Lestou et al., 2008).

Here, we will first use body motion tracking in interactive settings to acquire naturalistic stimuli of human actions. We will then generate a stimulus set of actions in which some actions will have the same form and a different goal, and others will have the same goal and a different form. Next, in behavioral experiments, we will ask participants to perform two different tasks on these stimuli: to identify the goal or the form of movements. After equating the two tasks for difficulty level, we will use them in a functional MRI experiments to identify and contrast the brain regions that are involved in action form and action goal understanding.

Significance:

The findings from this work will help determine the underlying neural mechanisms of action understanding. Since action reading is an integral part of social interactions, the results of this research will have broader implications for understanding the neural underpinnings of normal as well as impaired social cognition.

Laminar BOLD signal changes during perception versus mental imagery (Martin)

Primary Objective: Our goal is to determine the laminar profiles in humans during perception and memory using sub-millimeter fMRI.

Background:

The cerebral cortex is organized into layers that can be identified by the different types of cells they contain. Neurophysiology studies have revealed that different cortical layers make distinct contributions to information processing. For example, certain layers, such as Layer 4 receive “feed-forward” input from sensory nuclei in the thalamus. Other layers, such as Layer 5, send putative “feed-back” signals to lower-level cortical areas. In non-human animals, different laminar responses during are seen perception, where feedforward signals are putatively greater, than memory, where feedback signals putatively greater. Laminar responses in humans have not been characterized because the typical spatial resolution of most fMRI sequences (~3 mm³) cannot distinguish different lamina. However, recent advances in high-field MRI have led to dramatic improvements in spatial resolution, such that sub-millimeter resolution functional neuroimaging is now feasible.

Significance:

The significance of the proposed research is expected to be an initial characterization of lamina-specific changes in the BOLD signal in humans as related to cognition.

Topographical Organization of Category-Specific Cortical Areas in the Human Temporal Lobes (Martin)

Primary Objective: We will test our hypothesis that regions of VTC showing preferential activation for specific categories of stimuli will show preferential intrinsic and task-evoked functional connectivity with distributed networks of brain regions specialized for processing category-relevant properties or information.

Background:

Topographical organization of category-specific regions in the human ventral temporal cortex (VTC) is remarkably consistent across individuals, including regions showing preferential activation for conceptual categories such as faces, animals, bodies, objects, tools, scenes, words,

etc. To date, the determinants of this organization are largely unknown. One possibility is that it is driven, in part, by differential intrinsic connectivity of these category-regions with other domain-specific brain areas critical for processing different types of category-relevant properties or information. This preferential intrinsic connectivity would then facilitate task-related co-activation of these regions underlying perceptual and conceptual processing.

Significance:

A competing theory to ours offers a radically different explanation for category-related organization in the ventral temporal cortex. This view holds that inherent differences in the visual properties associated with different categories of stimuli alone could underlie these topographical dissociations in the VTC through a bottom-up visual mechanism. However, this theory fails to account for several phenomena, such as topographical dissociations for stimulus categories that do not have any apparent systematic differences in visual properties, or typical category-related organization that has been observed across the VTC in congenitally blind individuals. We argue that, although a bottom-up visual mechanism is likely a contributing factor, category-related organization in the VTC is largely shaped by patterns of intrinsic connectivity of these regions with other distributed, functionally specialized brain regions. Our study directly tests this hypothesis, and importantly, it is falsifiable. Thus, our results should provide sound evidence either confirming or conflicting with our hypotheses, yielding critical insight into the nature of intrinsic cortical organization that underlies higher-level perceptual and conceptual processing in the human brain.

Elucidating the functional organization and topography of visual processing (Baker/Ungerleider)

Primary Objective: To elucidate the nature of visual representations along the dorsal and ventral visual pathways.

Background:

Visual processing in cortex proceeds along two major pathways (Ungerleider and Mishkin, 1982): i) Dorsal pathway, critical for visuospatial processing and ii) Ventral pathway, critical for object recognition. While the global nature of these pathways is well established, exactly how visual representations are transformed along each pathway and the extent to which those representations depend on experience remains unclear. Our overarching hypothesis is that the representation within any particular visual area is a product of its position within large-scale cortical circuits. Thus, representations in strongly connected areas will share more characteristics than those that only weakly connected. Experience shapes the system by taking advantage of the already existing connections and representations, making it possible to predict where changes will occur and how strongly they will be based on knowledge of each participant's neuroanatomy and functional response.

Significance:

While the basic characterization of the dorsal and ventral pathways is well established the details of the processing along each pathway remain to be fully determined. Characterizing the response of regions along both pathways to a wide range of novel and previously experienced visual stimuli will enable us to elucidate the organization of visual cortical regions and the nature of the representations and their transformation along each pathway.

The role of top-down processing in visual cognition (Baker/Ungerleider)

Primary Objective: To investigate the impact of top-down processing on visual cortex

Background:

It has long been known that top-down processes such as recalling memories or paying attention, affect our ongoing visual perception. Further, imaging experiments have demonstrated the involvement of visual cortical areas during imagery and working memory (e.g., Lee, Kravitz, Baker, 2012). However, until now, it is not clear what the role of visual cortex is during visual imagery or working memory.

Significance:

We expect that the visual cortex will be involved in maintaining visual information during imagery or working memory, and that the type of visual information maintained will be dependent on the functional characteristics of the different regions of visual cortex. These results will elucidate one step toward understanding the functions of visual areas when top-down signals interact with incoming visual information.

Body Representations in Cortex (Baker)

Primary Objective: To elucidate the nature of body representations along the dorsal and ventral visual pathways

Background:

Body parts are some of the most salient visual and biological stimuli in our environment. We look at others' postures, gaits, and actions to read their intentions. We use our limbs to interact with objects and people, make gestures, and perform goal-directed behavior. Thus, understanding the neural representations of body parts is one of the core elements in understanding vision, action, and social cognition in the brain. Visual processing in the brain is thought to proceed along two anatomically and functionally distinct pathways that originate in the primary visual cortex: a ventral pathway, often characterized as a 'what' pathway and thought to be critical for object vision, and a dorsal pathway, characterized as a 'where' or 'how' pathway that processes spatial information. Body representations are found along both pathways and the goal of this research is to understand the nature of these representations and how they differ between the two pathways.

Significance:

While representations of the body have been observed in many different cortical regions, the nature of those representations and their relevance for body perception or body action remains unclear. This study will elucidate the similarities and differences between body representations in different regions.

Task-dependent representations in cortex (Baker)

Primary objective: To elucidate how observers' goals modulate object representations by examining how brain activity and behavior differs under different types of tasks.

Background:

One of the longest-standing questions in object recognition is how malleable object representations are to top-down cognitive factors. While behavioral studies suggest that knowledge, experience and expectations modulate the representations of objects, less is known about how "flexible" the neural object responses are, that is, how are they modulated by such top-down factors.

Significance:

The proposed study addresses a fundamental question in neuroscience, namely, how hard-wired and modular are neural representations of objects and how susceptible they are to changes in the goals of the observers. Ultimately, this study will elucidate the extent to which visual

object recognition transcends stimulus-driven hierarchical processing and is influenced by top-down factors, such as task, experience and goals of the observer.

Deconstructing visual scenes in cortex (Baker)

Primary Objective: To understand the unique contribution of object- and scene-selective regions to distributed scene representations.

Background:

Real-world visual scenes are enormously rich stimuli containing many different sources of information including spatial layout, local objects and semantic associations. Accordingly, there are two major challenges for understanding how scenes are represented in the brain. First, several cortical regions are engaged when people view scenes, and the question is how each region contributes to scene processing. Second, the complexity of scenes makes it difficult to tease apart the factors underlying the response of a region.

Significance:

The current studies will answer fundamental questions regarding the nature of scene representations. What constitutes a scene? Are objects the basic units of scenes? Can a group of objects with no background be considered a scene? Is semantic content necessary for scene perception? The minimal scenes approach in conjunction with different methodologies (fMRI, eye-tracking), has enormous potential to advance our understanding of the interactions between objects and spatial layouts.

Using eye-movements to investigate the representations of faces, objects, and scenes (Baker)

Primary Objective: To elucidate the perceptual processing of complex stimuli using eye movements as a marker of attention.

Background:

When viewing visual stimuli people make a series of eye movements. These eye movements are thought to reflect attention and can provide an index of the information being processed. Studies of eye movements have been used extensively in studies of reading but have also been examined during face and scene perception. In this study we will use eye movements to understand the processing underlying perception of complex visual stimuli.

Significance:

By contrasting eye-movement and behavioral measures between conditions, we can elucidate what features of the stimuli are critical for perceptual processing. These differences will indicate important differences in the spatial and temporal distribution of visual attention for various stimuli, tasks, or groups.

Representation of visual word forms in cortex (Baker)

Primary Objective: To elucidate the nature of the representations in cortical regions selective for visual words.

Background:

Prior studies have identified a region of visual cortex that appears specialized for the processing of visual words, often termed the Visual Word Form Area (VWFA) (Cohen and Dehaene, 2004). Responses in this region are stronger for visual words compared with many other types of visual stimuli and the selectivity observed is dependent on experience with the written script (Baker et al., 2007). It has been proposed that word processing along the ventral pathway comprises a hierarchy of feature detectors each tuned for progressively larger word fragments (letters → bigrams → quadrigrams) (Dehaene et al, 2005). This study will test this hypothesis comparing

neural representations for words varying in constituent letters, semantics and visual features (e.g. font) along the ventral pathway.

Significance:

By comparing responses to a wide variety of different words, we can elucidate what features of visual words are represented within different parts of the visual processing hierarchy.

Neural circuits underlying word and sentence reading (Martin)

Primary Objective: To determine the neural substrates and mechanisms underlying how we read words, phrases, and sentences

Background:

Investigating how the brain processes words and sentences involves gaining an understanding of both semantic and syntactic processing mechanisms. The study of semantics has thus far demonstrated a dissociation in the neural substrates for different categories of things (for a review, see Martin, 2007). Knowledge of tools, scenes, social, and emotional information are stored in different parts of temporal cortex, and this information can be accessed using words (Simmons et al., 2010; Herve et al., 2013). How these words are bound together through syntactic operations has been proposed to rely on separate neural circuits (Pallier et al., 2011) including substrates in left temporal and frontal cortices. But some of these neural substrates for semantics and syntax seem to be overlapping – specifically, social/emotional knowledge and syntactic processing both are proposed to lie in the left anterior temporal lobe. Interestingly, this may reflect the fact that syntactic studies nearly always use social sentences, while object sentences have rarely been investigated. Thus it is not known if the anterior temporal lobe also processes object sentences or if this is done elsewhere. We propose to resolve this seeming inconsistency by studying the neural bases in both the domains of space and time (through fMRI and MEG experiments) when reading different types of sentences.

Significance:

Results from these studies will help us come up with a more integrative framework for understanding the neural bases for semantics and syntax.

Human Auditory Mapping with High Magnetic Field Strength fMRI (Bandettini)

Primary Objective: To identify reliable maps of sound processing in human auditory cortex.

Background:

Studies using traditional fMRI methods have largely failed to produce reliable maps of individual fields in human auditory cortex, even at high magnetic field strengths. This failure is due primarily to a narrow focus on just a single dimension of organization in auditory cortex – the well-known dimension of tonotopy. Recent research in animal models suggests that primary auditory cortex is organized in two orthogonal spatial maps – a tonotopic map that responds preferentially to spectral frequency in order from low to high, and a periodotopic map that responds preferentially to temporal modulation frequency in order from low to high. This organization parallels the visual system in which individual field maps (e.g., V1) contain orthogonal representations of eccentricity and polar angle. Well-accepted methods for visual field mapping in fMRI measure these orthogonal gradients, using reversals in the representations of eccentricity and polar angle to delineate the boundaries of individual field maps. Recent work at relatively low spatial resolution has been able to identify the presence of 11 tonotopic and periodotopic maps in core and belt auditory fields within human auditory cortex. Still, the level of detail in these maps is low given limitations in spatial resolution. In this project, we will examine maps of tonotopy, periodicity, and other sound properties in the human brain using 3T

and 7T MRI scanners. We will use our high strength (7T) scanner to push the spatial resolution to values in the vicinity of 1mm³ isotropic. This corresponds approximately to one order of magnitude improvement in spatial resolution as compared to prior studies.

Significance:

This experiment will allow us to extend our understanding of the organization of human auditory cortex – namely, we will be able to move beyond macrostructural organization to a more detailed characterization of the functional properties within individual cortical fields. It will also help us evaluate the adequacy of high strength/high resolution fMRI to obtain this level of fine-grained information about the functional organization of the brain in a system other than visual cortex.

Is curvature processing functionally related to face processing (Ungerleider)

Primary Objective: To answer the question whether curvature processing is functionally related to face processing and whether the input to the face processing network originates from the curvature processing network.

Background:

It has been demonstrated for the first time in macaques that an anatomically segregated network of cortical regions prefers curved shapes to rectilinear shapes (Yue et al., 2014). This network includes three separate regions, partially overlapping the face-processing network. This overlap raises the question of whether curvature processing is functionally related to face processing, and whether the input to the face processing network originates from the curvature processing network. A behavioral and fMRI task are being proposed to investigate this hypothesis.

Significance:

Results from this experiment will provide fundamental insights into how face information is extracted and processed in human visual cortex.

Neurocircuitry involved in the representation of food (Martin)

Primary Objective: To examine the representation of taste and food-related stimuli in sensory and association regions of the human brain.

Background:

Grounded theories of cognition claim that the representation of objects within the brain occurs within the neural systems involved in the perception of those objects (Martin, 2015). Thus, the representation of a particular food within the brain should involve regions associated with the sight, taste, and smell of that food. Accordingly, merely viewing pictures of food (vs. non-food objects) activates primary taste-responsive regions of the human insular cortex (Simmons et al. 2005, 2013). While studies such as these have demonstrated the presence of multisensory food-related information in putatively primary cortical sensory areas, much still remains unknown about the content of that information. Specifically, do the patterns of activity present in cortical taste areas to visual food stimuli represent specific taste property inferences (i.e. sweet, salty, or sour taste), or do they reflect the more general salient properties of the depicted foods (i.e. pleasantness or aversion)? To address these questions, in this project we will examine the multi-dimensional representation of food-related stimuli within the brain, using a variety of behavioral and neuroimaging techniques.

Significance:

This project will further our understanding of the representation of food-related information in the human brain, as well as the functional organization of cortical regions involved in food perception.

How does the brain differentially represent visual information that informs action planning? (Ungerleider)

Primary Objective: Characterize the similarity of the neural response in both the dorsal and ventral streams to the grasping similarity determined behaviorally using the kinematics of the grasp and visual similarity ratings.

Background:

Early evidence from targeted brain lesions in non-human primates and brain damage in humans indicates that the primate visual system is divided into two pathways: one projecting dorsally from primary visual cortex to parietal cortex involved in action execution, and the other projecting ventrally to temporal cortex implicated in object recognition (Ungerleider & Mishkin, 1982; Goodale & Milner, 1992). The role of the dorsal visual pathway in perception has since been revised but has been assumed to be fundamentally action-associated (Kravitz et al, 2013). Recent studies seem to challenge this assumption based on findings of object responses in the dorsal stream that are similar to responses in the ventral stream (Konen & Kastner, 2008; Vaziri-Pashkam & Xu, 2017; Freud et al, 2017), *i.e.* being size, position, and view-invariant (Konen & Kastner, 2008) and occurring even in the absence of a motor task (Konen & Kastner, 2008). Thus, object processing—previously thought to only occur in the ventral pathway—has been recently been proposed to occur in the dorsal pathway as well (Freud et al, 2017). The current proposed project uses a combination of kinematics, behavioral ratings, and neuroimaging (fMRI, described below, or possibly MEG and/or EEG) to investigate whether the responses to objects found in the dorsal stream are related to action-relevant visual features or other visual features. Similar methods have been used by others (Fabbri et al, 2016) but their study did not dissociate the motor and visual aspects of the response. We aim to study visual and motor representations separately. Further, they used simple objects that did not nearly approximate the rich visual diversity of real objects. In contrast, in our design, we aim to study the representations of a rich set of natural objects in the context of grasping actions in the dorsal and ventral stream.

Significance:

The proposed research will further our understanding of how objects are represented both in parietal cortex and in the brain more widely by dissociating action-relevant from purely visual features of the objects. Further, many studies of human perception focus on highly artificial visual stimuli. This experiment aims to study more naturalistic perception using real objects in the MRI scanner, which is more ecologically valid without compromising experimental control.

E. Plasticity and Priming

What are the structural and functional correlates of learning visual associations? (Baker)

Primary Objective: To test the role of the uncinate fasciculus in mediating the learning of visual associations.

Background:

When we see a frying pan, we anticipate objects such as a kitchen stove to be present within the visual scene. How does the brain mediate the learning and representation of such visual associations? In non-human primates transection of the uncinate fasciculus (UF), a cortico-cortico pathway that links the temporal and frontal lobes, causes impairment in learning visuo-visuo associations, while object discrimination remains intact (Browning and Gaffan, 2008). Therefore, our hypothesis is that the ability to rapidly learn visual associations, and any learning-related changes in the structure of object representations will correlate with the architectural properties of the human UF.

Significance:

The findings from this study will help elucidate the importance of the structural connectivity between anterior temporal and frontal cortex and the neural representation of visual associations.

Measuring training-dependent structural plasticity in adults with advanced MRI techniques (Baker)

Primary Objective: To determine whether training-related structural changes in the adult brain can be reliably detected using advanced MRI techniques.

Background:

A growing number of MRI studies have reported presumptive structural changes in adult human (May, 2011). However, the robustness of the findings and the relationship to the underlying biological substrate are unclear (Thomas and Baker, 2012). In particular, the current human data do not provide rigorous statistical evidence and show limited replication. Thus, even though experience-dependent structural plasticity in the adult brain is thought to continue throughout the life span of an individual, the reliability of conventional MRI techniques to detect training-related plasticity has not been established. Further, conventional MRI techniques provide no means of quantifying structural changes.

Significance:

Demonstration of the potential for MRI to detect structural brain plasticity during training will have important implications for developing better rehabilitative therapies for traumatic brain injury (TBI) and other forms of brain injury.

Somatosensory perceptual learning (Baker)

Primary Objective: To explore the neural mechanisms underlying somatosensory learning.

Background:

The psychophysical, as well as the peripheral and central neural mechanisms that mediate tactile perception have been studied extensively. In the context of learning, human participants can readily discriminate tactile stimuli and show increased performance with training. However, in comparison with visual perceptual learning, the mechanisms of somatosensory perceptual learning are not well understood. An intriguing finding is that unlike visual perceptual learning, which is widely accepted to be specific to the trained location in the visual field, tactile learning has often been reported to transfer to the homologous finger on the untrained hand. In this study we will determine the limits of somatosensory perceptual learning in comparison with visual perceptual learning and investigate how learning may interact across the two sensory modalities.

Significance:

The behavioral and MRI experiments will help, (a) elucidate the temporal profile of learning, (b) establish the time course of retention of learning (c) determine whether the training effects transfer within and between hemispheres (d) explicate the mechanisms underlying functional remodeling of neural circuits in the trained and untrained hemispheres (e) and identify the white matter pathways critical for transfer of learning between hemispheres.

Effect of object repetition on neural tuning curves (Martin)

Primary Objective: Our goal is to evaluate the effect of object repetition on fMRI tuning curves (sharpening versus broadening) and identification speed/accuracy.

Background:

Experience with visual objects leads to later improvements in identification speed and accuracy (referred to as "repetition priming"), but generally leads to decreased rather than increased neural responses (referred to as "repetition suppression"). This relationship poses a basic puzzle: how is

it that reduced neural activity can cause improvements in behavioral identification? Recent physiological studies in humans using methods such as MEG and in animals using microelectrode recordings have suggested that enhanced neural synchronization between brain regions may be the mechanism that permits reduced neural activity to have a greater functional impact. Alternatively, reduced neural activity may have a greater functional impact due to changes in neural tuning, with cells responding more selectively to individual stimuli while they fire at lower rates to most stimuli (referred to as "sharpening"). Neural tuning can be assessed indirectly in human fMRI through the use of the "fMRI-Adaptation" paradigm, in which localized, automatic, and short-term neural response decreases are induced by brief, repeated exposures to an adaptor or "anchor" stimulus. The recovered response to a new or "deviant" stimulus is then thought to indicate how much overlap exists between the cell populations that represent the anchor and deviant stimuli within a given fMRI voxel. Sharpening predicts that less overlap should exist between the neural representations of stimuli that have been repeated over an extended duration/delay, with a fully (or nearly) recovered response to a related deviant stimulus (e.g. "cat" when the anchor is "dog"). In contrast, if repetition leads to greater representational overlap (as might occur in brain voxels/regions that encode conceptual relationships), the adapted response should persist to a related deviant stimulus (i.e. "broadening").

Significance:

The relationship between object repetition and object tuning has rarely been examined in humans, much less in conjunction with behavioral measures of improvement in object identification. The joint observations of decreased BOLD response for previously named anchors, larger recovery to related deviants, and improved identification performance of the anchors would be taken as support for the sharpening proposal. In contrast, the observation of weaker recovery to related deviants would be taken as support for representational broadening, a state that does not obviously support improved stimulus-specific identification responses but may support improved generalization of conceptual knowledge.

Effect of object repetition on neural response magnitude, regional interactions, and identification performance (Martin)

Primary Objective: Our goal is to evaluate the three-way relationship between neural response magnitude (BOLD fMRI) to object repetition, covariation of single-object responses across pairs of brain regions, and speed/accuracy of object identification.

Background:

Experience with visual objects leads to later improvements in identification speed and accuracy (referred to as "repetition priming"), but generally leads to decreased rather than increased neural responses (referred to as "repetition suppression"). This relationship poses a basic puzzle: how is it that reduced neural activity can cause improvements in behavioral identification? Recent physiological studies in humans using methods such as MEG and in animals using microelectrode recordings have suggested that enhanced neural synchronization between brain regions may be the mechanism that permits reduced neural activity to have a greater functional impact. In fMRI, this makes the surprising prediction that repeated objects should elicit weaker neural responses than non-repeated (or "novel") objects in task-responsive brain voxels while simultaneously showing greater correlation/covariation of neural responses between pairs of responsive voxels. Furthermore, these changes should be associated with improvements in measures of identification speed and/or accuracy.

Significance:

The relationship between mean BOLD response and the correlation of single-trial responses in an experimental condition has never been examined directly, in part because most researchers have utilized a more standard rapid event-related design that does not permit the isolation of single-trial responses. The joint observation of decreased mean BOLD response, increased correlation of the single-trial responses, and faster, more accurate naming with object repetition would suggest that neural synchronization is the mechanism that mediates improved identification in the face of overall decreases in activity.

The mechanism of emotional memory consolidation and reconsolidation

Primary Objective: To determine the neural substrates for consolidation and reconsolidation of emotional memories.

Background:

A growing number of studies have suggested that newly developed memories become stable through a consolidation process, and can be modified or updated up to several hours after retrieval through a reconsolidation process (Nader et al., 2000; Lee et al., 2008; Schiller et al., 2010; Sevenster et al., 2013). Until now, most consolidation and reconsolidation studies have focused on the hippocampus or amygdala. Moreover, few human studies have clearly elucidated the neural substrates for consolidation or reconsolidation. However, given that multiple cortical areas are activated during learning and retrieval especially in humans, these activated cortical areas may also be critical and serve as substrates for memory consolidation, and reconsolidation. In particular, it is still controversial whether the nature of consolidation and reconsolidation of emotional memories is different from that of neutral memories.

Significance:

Results from this experiment will provide fundamental insights into the stabilization and reorganization mechanism of emotional memories across cortical regions. Moreover, it will also help motivate the effective development of interventions to treat PTSD or panic disorder by providing critical knowledge for modifying targeted fear memories.

How does the memorability of stimuli influence memory and perception? (Baker)

Primary Objective: To understand the degree to which the intrinsic memorability of stimuli influences neural processing during perception and memory.

Background:

Despite our diverse experiences, people surprisingly tend to remember and forget the same faces (Bainbridge et al., 2013) and scenes (Isola et al., 2011) as each other. Images in fact have an intrinsic *memorability* – a predictive value of the probability of being later remembered that is stable to changes in time (Isola et al., 2014) as well as image context (Bylinskii et al., 2015). Until now, memory research has largely ignored these stimulus-driven effects, even though memorability has shown to determine as much as half of a participant's memory behavior, and may exist as a confound in prior memory studies (Bainbridge et al., 2013). Studying memorability may thus help us disentangle what factors play a role in determining what our brain encodes into memory.

Significance:

The findings from this work will elucidate the transition between perception and memory – what causes certain perceived images to be successfully encoded into memory, while others are not? This will also have implications for understanding how the brain prioritizes and organizes information during perception. Lastly, this work may support future practical applications focused on measuring and altering the memorability of aspects of our world.

Using naturalistic and dynamic memory stimuli to investigate how the brain represents episodic memories over time (Baker)

Primary Objective: To understand how the brain represents memories at different temporal and spatial scales (from one day to several years), using naturalistic video stimuli.

Background:

Memory experiments in a laboratory setting often rest upon stimuli that are highly rehearsed, artificial, or not personally meaningful (Maguire & Frith, 2003). However, recent neuroimaging work has begun investigating human memory by tapping into autobiographical memory, or specific memories from a person's life. Current methods mainly focus on cueing participants with text from a story about their lives (Svoboda et al., 2006), or having participants wear a "lifelogging" camera for a few days to a few months that takes random pictures of their lives to serve as stimuli (Nielson et al., 2015). However, story-based methods require the participant to re-encode the memories soon before the study, and these recently recalled stories may not serve as an objective measure of those memories. At the same time, lifelogging studies are limited in duration and naturalness, as it is practically difficult to have participants wear a device for more than a few months continuously, and it may affect participants' activities as they have little power over what images are taken of their life.

One recent trend in mobile applications (apps) and social media is the regular documentation of photos, sounds and videos of one's life over a long period of time. With the widespread usage of image- and video-sharing social media sites like Instagram and YouTube and the improvement of mobile camera quality and data storage, many people take photos, sounds, or videos of their life on a daily basis. These photos, sounds, and videos may serve as a unique, untapped, and rich collection of naturalistic memory stimuli. For example, one app entitled *1 Second Everyday* (<http://www.1secondeveryday.com>) has its users record one second of video every day that represents a salient event from that day. One second is able to capture rich information such as movement, sound, location, etc., and serves as a strong cue for memories for that day. At the same time, because of the briefness of a second, users are able to collect a vast amount of memories – one year of memories lasts about 6 minutes, while a lifetime lasts around 7 hours. There are over one million users of this app in the United States alone, and as this app has existed since 2012, there are also many users with multiple years of continuous "1-second" clips. This, and other similar applications may thus serve as novel, unique collections of participants with hundreds or thousands of naturalistic memory stimuli that could help probe new questions about memory representations in the brain.

Significance:

This unprecedented collection of naturalistic memory stimuli would help answer many memory questions previously unexplored – how is the time scale or spatial scale of a memory at encoding represented in the brain? What differences exist between more recent memories and older ones consolidated into long-term memory? Due to the richness of the stimulus set, we can also investigate questions related to emotions and memory, multimodal (e.g., visual and auditory) representations of memory, stimulus features that influence later memory, and whether a memory can be uncovered from the brain even if it is subjectively forgotten.

Which brain regions and circuitry mediate visual statistical learning? (Ungerleider)

Primary Objective: To understand the neural mechanisms of visual statistical learning.

Background:

Extracting and responding to the statistical regularities in the sensory environment has been a hallmark in the evolution of animals. These capabilities have helped in their survival and in

understanding the natural sensory environment around them. Extraction of these regularities is defined as “statistical learning” (Saffran et al 1996; Turk-Browne 2012). Humans have used the learned regularities in their sensory environment in a multitude of tasks, such as weather prediction, navigation, language acquisition, and music. While learning these regularities, humans not only learn to associate different sequentially occurring stimuli with temporal regularities, they also assimilate various abstract rules governing their occurrence, like transitional probabilities and embedded patterns. There have been many studies looking at various statistical regularities that can be learned (for reviews see Dehaene et al. 2015; Fitch and Friederici 2012; Krogh et al. 2012; Perruchet and Pacton 2006; Turk-Browne 2012) but little is known regarding the different neuronal mechanisms involved in learning these regularities. In this study, we aim to uncover the brain regions and circuitry that mediate visual statistical learning using behavioral and neuroimaging techniques.

Significance:

Results from this project will help elucidate the brain regions that mediate the learning of statistical regularities. This work will also guide the design of future electrophysiological recording experiments in nonhuman primates focused on areas revealed in the imaging project.

What are the neural correlates of novel skill learning? (Baker)

Primary Objective: To elucidate the neural correlates of novel motor skill learning

Background:

Studies of motor learning have revealed changes in different brain regions (e.g. primary motor cortex, cerebellum, striatum) associated with both the early and late stages of learning new motor behavior (e.g. Ungerleider et al, 2002; Doyon et al, 2002). These studies have often focused on tasks such as sequence learning or grip force control, which involve typical motor movements and strategies. Here we will investigate the motor and neural correlates of learning a novel motor skill, which requires the recruitment of new motor mechanisms. Specifically, we will study how the brain adapts to meet the cognitive and motor demands of a wearable robotic device (Makin et al. 2017) similar to the prosthetics that are worn by amputees. Learning to use a prosthetic device can be especially difficult (Østlie et al. 2012) because subjects must abandon motor kinematics usually invoked by controlling the hand. We will focus both on changes in motor representations in the brain as well as representations of the body and the prosthetic device. Prior studies focused on tools have suggested that with learning, tools can be incorporated into the body schema becoming represented similarly to a body part (e.g. Maravita and Iriki, 2004).

Significance:

The findings from this work will expand the basic understanding of motor learning and body representations, specifically as it relates to novel skills. This will be the first study of this nature to assess the impact of wearable robotic devices on body representation, with immediate implications for the basic understanding of body representation for psychologists, neuroscientists, clinicians and philosophers. Ultimately, these findings will provide valuable insight on how to optimize prosthesis rehabilitation training paradigms and the technical specifications of prosthetic devices to best meet the needs and abilities of prosthesis users.

Moral and Social Cognition

The neural systems responding to care-based transgressions as a function of severity (Blair)

Primary Objective: To determine whether the severity of care-based transgressions predicts activity within VMPFC.

Background:

Understanding the neural systems mediating moral cognition is important because the

impairment in moral cognition is central to understanding psychopathy (Blair, 1995). However, relatively little is known about the systems that respond to care-based transgressions (e.g., one person hitting another; in some respects the prototypic moral transgression). Arguments have been made that judgments about care-based transgressions are based on emotion (Blair, 1995) and that the neural systems that respond to such transgressions (e.g., ventromedial frontal cortex) do so because of the role of this system in emotion (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001). If this is correct, it predicts that more severe care-based transgressions will elicit greater activity within VMPFC than less severe transgressions. The current study tests this hypothesis.

Significance:

Results from this experiment will help to identify the neural systems responding to care-based transgressions and determine whether these systems show increased activity as a function of transgression severity. Impairment in moral cognition is central to understanding psychopathy (Blair, 1995). As such understanding the neural systems mediating the response to care-based transgressions may prove critical in allowing us to understand this disorder.

The neural systems mediating the distinction between care-based and conventional transgressions (Blair)

Primary Objective: To determine the neural systems responding to care-based as opposed to conventional transgressions and the influence of rule context on these systems.

Background:

A distinction between care-based (“one person hits another”) and conventional transgressions (“one person talks in class to another”) has long been made (Smetana, 1981). Specifically, in situations where there are no rules explicitly prohibiting a transgression, care-based transgressions remain prohibited. However, conventional transgressions are much more likely to be allowed. A failure to understand this distinction is one of the distinguishing features of psychopathy (Blair, 1995). However, little is known about the neural systems that mediate this distinction. Moreover, nothing is known about how rule context alters the neural representation of care-based and conventional transgressions. The current study examines this issue.

Significance:

Results from this experiment will help to identify the neural systems responding to care-based as opposed to conventional transgressions and how rule context influences the function of these systems.

The impact of audience on the neural response to care-based and conventional transgressions (Blair)

Primary Objective: To determine the impact of audience on the neural response to care-based and conventional transgressions.

Background:

A distinction between care-based (“one person hits another”) and conventional transgressions (“one person talks in class to another”) has long been made (Smetana, 1981). A failure to understand this distinction is one of the distinguishing features of psychopathy (Blair, 1995). However, little is known about how the presence/ absence of audience influences the neural response to these different types of transgression. There have been suggestions that its impact is considerably greater for conventional relative to care-based transgressions (Beer, Heeray, Keltner, Scabini, & Knight, 2003) but how this is manifested in the brain remains

unknown. The current study is intended to determine this.

Significance:

Results from this experiment will help to identify the neural systems responding to care-based as opposed to conventional transgressions and how audience presence/ absence influences the function of these systems.

The neural mechanisms of social provocation (Blair)

Primary Objective: To determine neural processes underlying human response to social provocation.

Background:

The neural mechanisms underpinning human cooperative behavior remain poorly understood. Previous work has shown increased striatal response when punishing unfairly behaviors, even when this punishment has a cost to the participant (de Quervain et al., 2004; Strobel et al., 2011). This response has been interpreted as a reward response and the basis of altruistic punishment (de Quervain et al., 2004). However, work in children has suggested that i) reward-related regions outside the striatum (e.g. ventromedial prefrontal cortex) do *not* show increased activation when punishing unfairness and ii) punishing unfairness is associated with increased activation in regions associated with reactive aggression responses.

Significance:

Results from this experiment will give insight into the emotional response associated with social provocation; namely, does punishing unfairness represent a reactive aggression response to threat or is this response inherently rewarding and the basis of altruistic punishment? Understanding the basis of response to social provocation will give insight into the overly hostile responses to social provocation associated with Conduct Disorder, Antisocial Personality Disorder, PTSD and other anxiety disorders.

The impact of animacy on threat processing (Blair)

Primary Objective: To determine the impact of animacy information on the processing of looming and receding threats.

Background:

Previous work has shown that increasing proximity of threat increases activity in regions associated with threat response, including periaqueductal grey and amygdala (Mobbs et al., 2007). Other work has shown that fear conditioning occurs more readily to animate relative to inanimate stimuli (Mineka & Zinbarg, 2006). It is unclear, however, how these two classes of stimulus features interact.

Significance:

Results from this experiment will provide insight into the nature of fear and threat processing. Understanding of these basic processes may have important implications for understanding anxiety disorders, particularly phobias and inappropriate reactive aggression responses, which are associated with a number of psychiatric conditions including PTSD, Conduct Disorder and Antisocial Personality Disorder.

F. Methods development and evaluation

Comparing uni- and multivariate statistical analysis (Averbeck)

Primary Objective: Our goal is to examine the multivariate statistics of the fMRI response for large-voxel-count regions of interest (ROIs).

Background:

There has been considerable interest recently in using multivariate pattern classification methods to analyze functional imaging data. This approach, also known as decoding, is often compared to standard general-linear model (GLM) or mass-univariate approaches. These two analysis techniques are, however, analytically related via a quantity known as the noise covariance matrix. The relative advantages of either technique can be examined in detail. This is often done heuristically by comparing the results of significance tests, but it can be done analytically by examining the structure of the noise in the data and its relationship to the signal in the system. Further, the relationship between the signal and the noise in the system can provide insight into why one or the other approach might be superior.

Significance:

While claims of the superiority of multivariate pattern recognition vs. standard univariate statistics have often been made, the assumptions under which this would be true have never been investigated. By examining carefully the multivariate statistics of the neural response we can clarify this relationship.

Multivariate analysis fMRI experiments (Bandettini)

Primary Objective: Our goal is to find the difference and similarity between patterns that are activated under different tasks or cognitive states in the whole brain or some regions of interests (ROI).

Background:

There has been increasing interest in multivariate pattern classification of fMRI data. In contrast with the conventional mass-univariate approach that aims to find the brain regions that correlate with the experimental conditions, the goal of the pattern recognition approach, also known as the decoding framework, is to predict the experimental stimuli and cognitive state from the brain activation patterns. The conventional method relies on the modeling of hemodynamic response (HRF), but the classification approach can detect subtle changes in activation patterns that may not fit the HRF model (Chu et al., 2011b).

Significance:

Multivariate pattern classifiers for fMRI can discriminate patterns of activation from different categories of tasks or stimuli, even when conventional methods show no statistical difference in the contrast of conditions. We can also use the patterns classifiers to identify similar cognitive states or changing of states.

Development and evaluation of perfusion imaging sequences (Bandettini)

Primary Objective: To examine the performance of PASL and PCASL with functional tasks at 3T and 7T. Secondary objective: To compare the performance of ASL and BOLD with functional tasks at 3T and 7T.

Background:

Various arterial spin labeling (ASL) techniques have been applied to measure resting and functional cerebral blood flow (CBF). CBF provides physiological information complement to BOLD and related to the health and changes in brain functions. However, due to certain limitations, the success in applying ASL relies on proper selection of pulse sequence parameters and appropriate assumption in quantification. Pulsed ASL (PASL) has the shortest temporal resolution and highest tagging efficiency but suffers from limited tagging volume, hence low SNR (Luh et al., 2008). Pseudo-continuous ASL (PCASL) provides well-defined tagging volume (Dai et al., 2008) but has velocity-dependent and inhomogeneity-sensitive tagging efficiency (Luh et al., 2008). Therefore the selection of ASL techniques and pulse sequence parameters

should tailor to experimental design and target brain regions. By systematically varying task frequency using both PASL and PCASL techniques among different target brain areas, the performance of ASL can be examined.

Significance:

With systematic examination of crucial parameters in applying ASL techniques to fMRI studies, important factors can be identified and tailored to specific brain regions and the requirements of temporal resolution of functional tasks. With proper application of ASL techniques, reliable measurement of baseline CBF and CBF changes can be obtained during resting and functional tasks for normal and pathological states.

fMRI calibration and non-neural noise removal (Bandettini)

Primary Objective: With systematic examination of crucial parameters in applying ASL techniques to fMRI studies, important factors can be identified and tailored to specific brain regions and the requirements of temporal resolution of functional tasks. With proper application of ASL techniques, reliable measurement of baseline CBF and CBF changes can be obtained during resting and functional tasks for normal and pathological states.

Background:

fMRI ideally measures relative changes in regional brain metabolism. Still many other factors can also cause fMRI signal changes. Any variation in blood flow, blood oxygenation, vessel density, or neurovascular coupling will alter fMRI responses. These variations can be caused by something as simple as heart beats to complex vascular changes with aging and medications. For studies of healthy volunteers, non-neural factors that alter fMRI responses are just added noise. For studies across populations, a systematic variation in any of these factors might create systematic population biases. There are existing methods to remove some heart rate and respiration changes over time (Glover, Li et al. 2000; Birn, Diamond et al. 2006; Chang, Cunningham et al. 2009) and reduce noise in the actual data for a study. Calibration methods usually require separate scans that will be used to calculate a voxel-wise or whole brain magnitude correction (Bandettini and Wong 1997; Davis, Kwong et al. 1998; Hoge, Atkinson et al. 1999; Handwerker, Gazzaley et al. 2007). All these methods have limits. The heart rate and respiration corrections are imperfect. For example, no existing method accounts for common events, such as spontaneous breath holding. The calibration methods are often impractical and require multiple runs of breathing CO₂ enriched air (Hoge, Atkinson et al. 1999) or rely on less precise manipulations like breath holding (Handwerker, Gazzaley et al. 2007). We are examining the existing methods and designing new ways to remove non-neural fMRI signal fluctuations.

Significance:

Improved calibration and noise removal methods will increase the accuracy of fMRI studies particularly resting connectivity. In addition, removing non-neural signal biases across populations and individuals will improve fMRI's utility for understanding neural changes and diagnosing diseases and disorders.

Real time fMRI methods development (Bandettini)

Primary Objective: The primary objective of this study is to determine how much neurofeedback training is retained between sessions and the secondary objective is to determine how much training is required to maintain voluntary control of this region.

Background:

In real-time fMRI (rt-fMRI) the data is analyzed immediately enabling applications such as fast functional localization and quality assurance. In particular, it is possible to give feedback to the

person undergoing the fMRI scan about their current brain state. Recent papers have shown the ability to train subjects to control the level of activation in specific regions of the brain such as the amygdala (Posse et al., 2003), insula (Caria et al., 2007), and anterior cingulate (Weiskopf et al., 2003) regions by using rt-fMRI neuro-feedback. This technique has the potential in future applications for brain computer interface development or clinical interventions for reduction in anxiety or improved emotion control. Many facets of this relatively new technique remain unexplored such as the duration of training and the brain regions involved in up-regulating specific parts of the brain.

Significance:

The ability to maintain voluntarily control of the activity in selected brain regions will have implications in the treatment of patients with emotional regulation problems such as PTSD or depression. These patients may be able to be trained in the scanner to reduce their anxiety, which may translate into an improvement in their everyday lives. This intervention may augment cognitive therapy and mitigate their reliance on psychotherapeutic drugs.

Long resting state scans for development of clustering methods (Bandettini)

Primary Objective: To better understand the temporal scale of cognitively meaningful changes in whole-brain connectivity.

Secondary objective: To gain a better understanding of how task performance disrupts whole-brain resting-state connectivity patterns.

Background:

The analysis of spontaneous low frequency signal fluctuations in BOLD time-series has proven very fruitful for the study of the normal, diseased and aging brain. Because a single 5 – 10 minutes no-task scan can provide information about the functional organization of the whole brain, this fMRI modality is suitable for the clinical environment where time and subject compliance are limited. Until recently, most resting-state fMRI (rs-fMRI) studies have assumed stationarity of the functional organization of the brain in the time scale of several minutes. Recently, this assumption has been challenged by several studies showing how patterns of connectivity within distal brain regions change at a faster scale (tens of seconds). Still, how often do these changes in connectivity occur, their actual temporal scale, their relationship to changes in cognition, or how they are affected by subjects engaging on tasks with different attention demand levels is not yet understood. Moreover, no consensus exists yet as to which analysis techniques are better suited to detect reproducible, yet dynamic, patterns of whole brain connectivity. The experiments described below try to address some of these open issues.

Significance:

These experiments are designed to acquire a better understanding of the temporal scale at which cognitively meaningful changes in whole-brain connectivity patterns do occur. We also expect to gain a better understanding of how task performance disrupts whole-brain resting-state connectivity patterns. For many years, investigators have reported abnormal regional activity patterns for specific tasks in relationship to different psychiatric disorders. In recent years, rs-fMRI have demonstrated how some disorders are better understood in terms of disruption of connectivity patterns between regions instead of only differences in localized activity. We hypothesize that yet other conditions maybe better understood by disruption of dynamic changes in connectivity patterns that happen during rest or as a result of shifting from rest to task or from one task to another. In this experiments we aim to define what are the normal ranges of dynamic behavior and what is to be expected from normal subjects both during rest and tasks experiments. Once these normal ranges, should they exist, are well defined, additional experiments with

clinical populations will need to be performed in order to evaluate the potential clinical relevance of any deviation from the norm.

Improved diffusion imaging stability and distortion reduction (Bandettini)

Primary Objective: The primary objective is to maximize the precision and accuracy of diffusion metrics by quantifying and decreasing non-axonal sources of signal variation. The secondary objective is to maximize the spatial accuracy of diffusion imaging by decreasing sources of image distortion.

Background:

Various diffusion imaging techniques are being increasingly deployed to probe brain micro-structure to make inferences about brain connectivity (for example, diffusion tensor imaging (DTI) based tractography). Most diffusion imaging techniques require collecting many brain volumes with different diffusion directions and magnitudes. Ideally, nothing changes between volumes except these diffusion directions and magnitudes. This allows the volumes to be combined to estimate clinically and scientifically relevant measures such as fractional anisotropy or diffusion probability density functions. These measures can be used to estimate the locations of axonal tracts in the brain (Jones, 2010).

Many factors including temporal instabilities in the scanner, subject motion including breathing and heart pulsation are issues for many types of MRI imaging, but diffusion imaging can be particularly sensitive to these issues. In addition, there are noise sources that are worse due to diffusion acquisition methods. Diffusion gradients create eddy currents. These eddy currents affect overall image stability through different diffusion weightings, and the differential distortions induced by the various diffusion weightings.

Diffusion imaging methods are limited by existing methods to decrease distortions and noise during acquisition, rapidly identify and fix or remove data during processing, and robustly create meaningful metrics of brain diffusion.

Several sub-experiments aimed at the following goals will be conducted:

1. Developing techniques to mitigate the effects of eddy currents on diffusion imaging quality and stability. The primary techniques used to deal with eddy currents use a variety of warping techniques, some field map based, some based on linear and non-linear warps to various structural image scans. Another technique acquires diffusion data with regular and opposing gradient polarity to generate images with distortions of opposing types, and then computes an “average” image in which the distortions are minimized (Holland et al., 2010). Other approaches involve reshaping of the diffusion gradient pulses to see if shapes like sinusoids or sigmoids can be used to more efficiently trade off time for eddy current reduction. Another option may include embedding multiple navigators into the imaging scheme to measure field maps at various points in the imaging process, and potentially correct for distortions based on these field maps. We will test and quantitatively compare these methods and others.
2. Examine the effects of other imaging acquisition options on the quality of diffusion metrics. As stated above, there are many options for numbers and combinations of diffusion direction and magnitudes. Given limits on volunteer time in the scanner, different options will be tested to achieve a balance of data quality and realistic scan duration. Other parameters such as voxel size and field strength also affect the parameter estimation and noise. Some diffusion sequences record pulse and make sure images are collected at the same point in the cardiac cycle. This also has the potential to decrease noise and increase stability.

3. Examine the effects of preprocessing steps including image reconstruction and undistortion approach, automated and manual identification of overly noisy volumes, and calculation methods for multiple diffusion imaging methods.

Significance:

Even with unsolved issues, like image distortion, diffusion imaging and tractography are already applied to pre-surgical planning, stroke and tumor diagnosis and treatment, and many other clinical conditions. They have the potential to have significant diagnostic and prognostic uses for traumatic brain injury. They are also increasingly useful to studies of brain development and plasticity. Finding ways to improve diffusion image quality is fundamental to improving existing applications and identifying new uses.

Can blood volume fMRI overcome limitations of BOLD fMRI? (Bandettini)

Primary Objective: To examine if the higher local specificity and quantifiability of blood volume sensitive fMRI can be used to overcome limitations of conventional BOLD fMRI methods.

Background:

It is known from invasive contrast agent based animal fMRI studies that blood volume change induced by neural activity is dominated by microvessels in close proximity of the neurons, while conventional BOLD fMRI is dominated by more distant large draining veins. Hence, blood volume fMRI using pulse sequences that do not require invasive contrast agents, like vascular occupancy imaging (VASO), might provide a more accurate mapping of neural structures compared to BOLD fMRI.

Furthermore, since BOLD is an indirect contrast that depends on the covariation of oxygen consumption, blood flow and blood volume it is harder to interpret. In this respect, blood volume fMRI might help to provide a better understanding of the vascular mechanisms of BOLD fMRI.

Significance:

The results will provide fundamental insights into how limits of conventional BOLD may be overcome with blood volume fMRI. This knowledge will help to expand the scope of fMRI methods to allow new research questions about the high resolution representation of brain processing.

How do inherent beliefs and biases influence continuous processing during naturalistic tasks? (Bandettini)

Primary Objective: To understand the degree to which internal states of participants influence the continuous neural processing during naturalistic tasks, and how naturalistic tasks may be used to predict present or future behavior at the level of individual participants.

Background:

While traditional fMRI experiments using block and event-related designs have been increasingly useful at identifying the underlying brain regions associated with different cognitive tasks, they have too often overlooked individual differences in behavior and brain activity between subjects (Finn et al., 2017; Finn et al., 2015). While many in the field have turned to resting state data, recent research has shown that naturalistic tasks (e.g. movies, continuous stimuli) outperform rest at measuring intra- and inter-subject correlation in functional connectivity (FC) measures, which are distinct at the individual level (Vanderwal et al., 2017). Furthermore, individual differences have been found to be augmented using repetition of stimuli or priming of stimuli using content adjacent or opposite of the stimulus of interest (Pugh et al., 2011). We believe that the combination of priming and naturalistic stimuli may allow us to examine the often overlooked individual

differences using metrics of functional connectivity and inter-subject correlation (Finn et al., 2018).

Significance:

The findings from this work will expand our understanding of how an individual's state of mind (whether inherent or primed) influences subtle variations in the continual brain response during naturalistic tasks. Previous work by our group has shown that a person's internal state can be measured during continuous tasks. It is still an open question as to how these variations relate to previously held beliefs towards a topic, whether they can be further modified using priming, and how they relate to various neuropsychological tasks and criteria. This work may support future practical applications on measuring bias, attention, and even clinical diagnoses.

Relationship between BOLD and on-going cognition with and without tasks (Bandettini)

Primary Objective: To advance our understanding of the joint dynamics of BOLD fluctuations and on-going cognition during fMRI scans by developing novel fMRI analytical methods that can uncover, characterize and model the contribution of experimentally uncontrolled cognitive and motor state changes.

Background:

As part of the experiment “Long resting state scans for development of clustering methods,” on page 47 of this protocol, we developed methods aimed at capturing how on-going cognition manifests in both task and rest fMRI recordings. For example, we evaluated how clustering of whole-brain dynamic functional connectivity patterns could help detect periods of distinct cognition both as dictated by external task demands, as well as during rest. Yet, our ability to validate those results is severely limited by the lack of detailed information regarding what mental, emotional and motor activities subjects engaged with during the scans, when and for how long. To ameliorate this issue and achieve the extended goals of the experiment, we propose to conduct phase II of this study with a series of task and rest scans; which this time will be annotated with measures such as subject-provided descriptions of on-going thoughts, mood, sensations, body motion and facial expressions at several moments during the scan as well as parallel measures of cognitive state such as EEG, eye tracking, electromyography, galvanic skin response, and body and face motion.

Significance:

These experiments will extend our understanding of how variations in on-going cognition, including alertness, mood and vigilance, affect measures of brain activity, static functional connectivity and dynamic functional connectivity during both rest and task scans; well beyond what we accomplished in our earlier phase I experiments. Ultimately, this newly acquired knowledge will improve our understanding of spontaneous BOLD activity and allow us to develop novel analytical methods to uncover, characterize and remove (if necessary) the variance contributed by experimentally uncontrollable mental, emotional and motor activities to fMRI recordings.

The outcomes of these experiments will also help us understand how covert experimentally uncontrollable mental states, emotions and motor activities contribute to inter-subject and inter-population differences in fMRI derivatives (e.g., activity and/or connectivity metrics). This in turn will provide us with the means to potentially model and account for their contribution so that other sources of clinically relevant variance can be more readably identified.

3. Subjects

a. Description of study populations

4100 healthy normal volunteers will be studied under this protocol. If there are any subject withdrawals or dropouts they will be replaced.

b. Inclusion criteria

Healthy adults, with at least a high school education, aged 18 to 65 years, will be recruited to participate in the study.

c. Exclusion criteria

- Subjects will be excluded if they:
 - are an NIMH employee or a relative
 - have evidence of, or a history of:
 - major medical, neurological or psychiatric illness
 - serious head injury
 - learning disability
 - drug or alcohol abuse or dependence in the past 3 months, except nicotine
 - are taking prescription drugs or supplements that may affect brain function
 - have serious vision or hearing problems
- In addition to the above, additional exclusion criteria apply for all MRI studies:
 - Female subjects who are pregnant or have a positive pregnancy test 24 hours prior to an experiment will be excluded from neuroimaging studies.
 - All subjects will be questioned prior to MRI scanning for possible occupational exposure to metal slivers or shavings, which may have become accidentally lodged in the tissues of the head or neck. Subjects with surgical clips or shrapnel in or near the brain or blood vessels, subjects with cochlear implants, subjects with any metallic body in the eye or CNS, and subjects with any form of implant wire or metal device which may concentrate radiofrequency fields will be excluded from MRI scanning experiments because of possible risks during MRI scanning. Those whose history is suggestive of such a problem will also be excluded from the MRI portion of the experiments. They may still participate in the behavioral and MEG experiments.
 - Subjects unable to lie flat on their back for up to 3 hours may not be eligible to participate in MRI scans.

4. Design and Methods:

a. Study overview

This protocol is designed to acquire behavioral, MRI and MEG data while subjects participate in many different cognitive experiments. Once enrolled, subjects will be contacted by study personnel via phone or secure email to participate in one or more experiments. Depending on the specific needs of the experiment, subjects may be asked to participate in behavioral experiments outside the scanner or inside the MRI or MEG scanners. Some experiments may only require one visit while others may require multiple sessions over a period of days, weeks or months. Subjects are free to participate in as many experiments as they wish. All experimental sessions will be conducted on an outpatient basis at the NIH campus. Each behavioral testing

session will last no more than 3 hours. MEG and EEG sessions will be limited to two hours per session. MRI scan sessions will be limited to 3 hours, no more than 2 sessions per day, and no more than 4 hours total per day. Subjects may concurrently participate in several experiments and there is no maximum on how many experiments they can participate in at a given time or period of time. On any given visit, participants will sign an “Acknowledgement of Participation Form” (see Appendix 25D) that states that the subject has previously consented to participate in the protocol and lists the procedures that he/she will undergo on that visit. This form will be saved in the subject’s file in a locked cabinet in a room that is locked when unoccupied.

b. Recruitment

Healthy controls will be recruited from the NIH campus, through the normal volunteer program, Research Match, and from the surrounding community. Pre-approved recruitment advertisements (see Appendix 25C-1) will periodically be posted on the NIH-IRTA list-serv called *Club-PCR*. Other material may also be used to advertise and recruit potential participants (see Appendix 25C-1). Other sub-study specific advertisement material (see Appendix 25C-2) will also be used. The written advertisements will be used in color as submitted, or may be printed in black and white. The color of the ads may vary. Color changes will not be used to change the emphasis of an ad.

The size of the ads may vary, but all parts of the ads, including fonts and pictures, will be changed proportionately to the rest of that ad. Disproportionate changes in size will not be used to change the emphasis of an ad.

Healthy volunteers will also be screened under protocol titled 17-M-0181- *Recruitment and Characterization of Healthy Research Volunteers for NIMH Intramural Studies*. Data obtained for a participant under the screening protocol will be used for this protocol.

Laboratory personnel including research assistants and postdoctoral fellows will contact potential subjects who have expressed an interest in volunteering, via telephone or secure email.

Subjects will be asked a set of pre-screening questions to determine eligibility for admission to the protocol. These questions will pertain to inclusion and exclusion criteria and are described in the Eligibility Checklist (Appendix 25A).

We expect that we may have a yearly accrual rate of about 150-250 subjects for all the experiments combined.

NIH Employees will not be directly recruited by or through their supervisors or coworkers to participate in this study.

c. Screening

If a subject meets the pre-screening criteria in Appendix 25A, a study investigator or IRB approved personnel will obtain consent before any further screening is conducted. Once the consent has been obtained, study investigators or their research assistants will collect further information such as demographic, education, handedness and relevant medical information to assist in determining their eligibility for further evaluation by our study Nurse Practitioner. If the subject has not already had a physical and neurological examination by an NIH physician within the last year, then such an exam will be scheduled and conducted by our study Nurse Practitioner.

d. Future Contact

During the screening and recruitment process individuals will be explicitly asked for permission to re-contact them in the future. Appropriate methods for such contact (e.g. phone, email, letter) will be determined at the time of consent. They will also be told that the information that they provide during the screening will be saved electronically on secure LBC servers that will be accessed by study investigators or their research assistants only.

e. Study Procedures

General Study Methods:

After screening, informed consent, history and physical and neurological examination (as indicated), subjects will be asked to visit the NIMH IRP for study participation.

Subjects are not required to participate in all the experiments under this protocol. They may participate in only one experiment or as many experiments as they wish. There is no time limit on when the different experiments need to be completed by. Depending on the experiments being run at any time and their willingness to participate, subject may make anywhere from one to 12 visits for each task.

A study investigator or his/her research assistant will schedule a subject to participate in an experiment at a mutually convenient time. For experiments requiring subjects to engage in behavioral tasks, subjects will be asked to practice the task prior to the experiment. For each experiment, the study investigator or his/her research assistant will obtain an “Acknowledgement of Participation Form” (see Appendix 24D) to participate in that particular experiment, and will describe the task and procedures (for example, behavioral task, MRI, MEG, eye-monitoring, physiological monitoring, questionnaires) at the first visit for that particular experiment.

There is no limit to the total duration of a subject’s participation. However, subjects should have had an NIH physical or neurological examination within the past year in order to continue to participate in this protocol. If the consent form changes anytime during the subject’s participation, a new consent will be obtained and stored with the subject’s medical record and a copy will be saved to the subjects’ file that is kept in a locked cabinet in LBC in a room that is locked when unoccupied.

Some of our cognitive tasks, tests and questionnaires, that do not require experimenter presence, will be run using Clinical Trials Survey System (CTSS) and Clinical Trials Database (CTDB). We will work with CTSS/CTDB administrators to create unique landing pages for our tasks, tests and surveys. We will direct subjects who are enrolled in our study to visit our secure CTSS landing page to complete tasks online. Subjects will be compensated at the same rate as in-person behavioral testing visits. For example, for a task that takes 30 minutes to complete online, participants will receive \$30 (\$20 for first hour + \$10 for inconvenience of cognitive testing). All data acquired will be stored securely on CTDB and then transferred to secure lab computers for additional analyses. CTSS and CTDB have been developed by NICHD/NIH and conforms to all NIH privacy, confidentiality and IT security requirements.

If participants are unable or unwilling to travel to the NIH, we may perform some procedures virtually. Specifically, the study team may obtain informed consent, perform history and physical

exams, and conduct some study procedures via tele- or video-conference. These virtual visits will use NIH approved modalities to engage with study participants and will adhere to NIH guidelines.

Neuropsychological Testing and Questionnaires:

Depending on the experiment subjects may be asked to fill out certain personality tests such as the Spielberger State Trait Anxiety Inventory (STAI) (Spielberger and Gorsuch, 1983), the NEO Five Factor Inventory (NEO-FFI), the Harm Avoidance Subscale of the Tridimensional Personality Questionnaire (TPQ-HA) (Cloninger et al., 1991; Costa and McCrae, 1992), the Liebowitz Social Anxiety Scale: Self Report (LSAS-SR) (Liebowitz, 1987), The Imaginal Process Inventory (Singer & Antrobus, 1966) and the Positive and Negative Affect Schedule (PANAS).

Subjects may also be asked to complete tests to measure IQ and other neuropsychological parameters, and parameters related to cognitive, executive, perceptual, social, affective and arousal domains (for example, BRIEF-A, Towers of London, N-back working memory task, Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS), Sensitivity to reward and punishment Scale, Social Responsiveness Scale-2 Adult Self-Report, etc.). These measures may be completed during a visit or at home, and either online, on a computer or on paper, depending on the nature of the test or questionnaire.

Behavioral Task Experiments:

Participants will be required to complete computer based tasks (each task is described in *Task Descriptions* section on Page 58 in detail) on one to 12 visits for cognitive testing, each lasting about an hour for most tasks. Some task may only require a visit for half an hour, while others may take up to 3 hours. Some learning experiments may require participants to complete up to 12 sessions of cognitive testing.

MRI scanning Experiments:

All scanning will take place in the NMR Facility at NIH on either 3T or 7T scanners.

Participants' will be given earplugs prior to entering the scanner. Upon entering the scanner, an RF coil will be placed around the subject's head. Participants' heads will be held in place by a standard head restraint method that may consist of soft foam, inflatable foam bags where the participant can directly adjust the pressure, a 'bite bar' (a mold of the upper teeth that helps to keep the head in the same spot - note, biting down is neither required nor necessary for the head restraint to be effective), a vacuum bag and/or hardened polyurethane foam (expanding packing foam). Additional physiological monitoring (e.g. ECG, respiration rate, non-invasive BP and skin conductance) may also be employed. A respiration belt may be used to measure respiration volume and a pulse oximeter to monitor heart rhythm. After the subject's head is positioned in the head holder, the patient will be moved into the tunnel-like scanner. During the scan, subjects will be able to hear instructions from the investigators via the loudspeaker inside the scanner room. They will also be able to communicate to investigators in the control room by speaking or pressing a call button.

During a scan the subject hears a loud rhythmic tapping or banging sound. This noise is caused by the switching of the gradient coils that is necessary to produce the brain image. Subjects are warned of this prior to scanning, and most find it only mildly objectionable. If subjects are unable to tolerate confinement for the necessary period of time, the scan is stopped.

Two types of MRI studies of the head will be obtained. High resolution MR images of brain structure will be obtained to correlate neuroanatomical structure with functional information obtained with functional MRI. Functional MRI studies will be obtained as a method for measuring local hemodynamic changes associated with perceptual and cognitive operations.

Structural and functional MRI scans will usually be obtained during the same scanning session. Time in the magnet will be approximately 2 hours and will not exceed three hours per scan session, with no more than two MRI scan sessions per day. In addition, if there are two scan sessions in a day, the total duration of the scans will not exceed 4 hours.

If a subject is unable to tolerate the scanner environment for the necessary period of time, the scan will be stopped.

Image data will be transferred to secure servers via the secure campus-wide network.

Structural MRI:

High-resolution MR images of brain structure, using MP-RAGE (Magnetization Prepared Rapid Gradient Echo), SPGR (SPoiled Gradient Recalled acquisition in the steady state), Diffusion Weighted Images (DWI) for white matter tractography, proton-density weighted MRI, and/or DESPOT (Deoni, Rutt, & Peters, 2003) sequences, will be obtained to determine morphology as well as to correlate neuroanatomical structure with functional information obtained with fMRI.

Functional MRI:

fMRI studies will be obtained as a method for measuring local hemodynamic changes associated with cognitive performance.

Subjects will be trained as necessary to perform each task and, depending upon the nature of the task, given an opportunity to practice before entering the MRI scanner. Training will first take place either at a desk or within the mock scanner or within the real scanner. A subject will perform one or more IRB-approved tasks that will test perception, attention, memory, emotion, problem solving, learning, social cognition and/or decision-making skills. Subjects will see visual stimuli on a screen and will indicate their responses on task trials using a response device such as a button box with his/her hand or by speaking aloud ((Birn, Cox, & Bandettini, 2004).

During resting-state MRI scan sessions subjects will be instructed to clear their minds and fixate on a black cross in the center of the screen. Since there is no single definition regarding what is “rest” in an awake individual, different studies give slightly different volunteer instructions. The instructions are consistent within each study. In all studies, volunteers are told to try to stay awake and keep their head as still as possible. In some cases, volunteers are instructed to clear their minds and fixate on a black cross in the center of the screen. In other cases, they are told to keep their eyes open or closed. Some studies use a very low level task, such as asking for infrequent button presses to help volunteers stay awake (Van Dijk et al., 2010).

In some sessions, MRI slice acquisition parameters may be adjusted to obtain optimal signal and coverage of areas of interest.

Magnetoencephalography:

The research subject will either sit or lie supine comfortably in a shielded recording room with

his/her head in a specially designed helmet. Brain magnetic fields will be recorded with the 275-channel OMEGA system. The 275 SQUID sensors are uniformly distributed, in a grid, over the inner surface of the helmet that covers the entire head with provisions for the eyes and ears. The MEG recording device is silent and subjects are not confined to a small space, therefore no claustrophobia should occur. Visual and two-way audio communication with the subject will be maintained throughout the session. Head position within the magnetometer will be determined before and after the MEG session by digitizing the position of three indicator coils that are attached to the preauricular and the nasion fiducial points. The positions define the coordinate system for the signals and allow for post-hoc correction of head movement artifacts. Digital photographs of the fiducial points will also be taken to localize the same points on the subject's anatomical MRI scan. All scans involve the presentation of visual stimuli while the subject is in the scanner and the subject responds by pressing buttons with the fingers of his/her hand. The subject can communicate with the control room personnel via an intercom at the operating console. The subject can be removed immediately from the scanner if necessary. Scan sessions will not exceed two hours.

Electroencephalography (EEG):

Standard

The participant will sit in a comfortable chair and a researcher will take measurements of the subject's head to identify the correctly sized EEG net and specify correct placement of the electrodes. Once the correct net is identified, it will be soaked in warm salt water solution for about 5 minutes (this makes it possible for the electrodes to measure the small (μ V) electrical currents generated by the brain). A researcher will then apply the electrode net to the participant's head. The electrode net is composed of soft 128 or 256 electrodes, each covered with a soft sponge, and held together with elastic. Electrode sensitivity (impedance) will then be measured and individual electrodes will be adjusted to optimize the signal recording. Participants will then perform a task involving visual, auditory, or tactile stimuli (see detailed list of sub-studies under the Task Descriptions section), while the subject's responses are recorded on a computer. The subject can communicate with the researcher at all times, and the experiment can be stopped immediately if necessary, and the electrode net can be removed in under a minute. Each experimental session will last no more than 3 hours.

Simultaneous EEG-fMRI

Setup for EEG combined with fMRI is similar to the standard procedure outlined above. In addition, a pair of EKG electrodes will be attached to the subject's torso using disposable adhesive electrodes that are approved for MRI use. After wearing the EEG net and EKG electrodes, the subject will then enter the MRI environment standard fMRI procedures are followed. In accordance with standard fMRI safety procedures, the participant will be monitored continuously and will be able to communicate with researchers in the control room at all times.

Simultaneous EEG-MEG

Setup for EEG combined with MEG is similar to the standard procedure outlined above for MEG except that an EEG electrode net will be placed on the participant's head. The net will be connected to an amplifier in the magnetically shielded MEG room. All other normal MEG procedures will be followed.

Pregnancy Testing for MRI scans:

The risk of MRI for a fetus has not been determined. Therefore, each female subject will be given a pregnancy test no more than 24 hours prior to any scheduled MRI scan. If the test is positive, the scan will not be conducted.

Individualized foam helmets:

For some neuroimaging experiments involving MEG or MRI, we may create individualized foam helmets to minimize head motion during data acquisition and to allow measurement of data from the exact same location across multiple experimental sessions. These helmets are based on a 3D reconstruction of the surface of a participant's head, which is created either by walking around the participant using a camera that can digitize the location of the head in space, or by extracting the surface of the scalp from a participant's structural MRI scan. The surface reconstruction (which does not contain any identifying information such as participant name, age, etc.) may then be sent to a helmet manufacturer, to create an MR safe foam helmet that closely matches the shape of the participant's head. Although designed to improve comfort, if the participant finds it uncomfortable, the scan can be stopped at any time and the helmet can be removed.

Eye tracking:

Some cognitive tasks during behavioral, MEG and EEG sessions, or MRI scanning will be administered in conjunction with eye-tracking. Eye-tracking involves the use of a special machine setup which records the location of the pupil. Eye-tracking may be done with a head-mounted set-up (a cap is attached to the head with infrared cameras placed in front of the eyes), or a column set-up (participants place their head into a column and look through a tilted glass screen, which enables the infrared cameras above to record their eye-movements through reflection).

During behavioral, MEG and EEG sessions, the eye-tracking system will allow the subject to comfortably place his/her head in a fixed position (using a chin-rest). During MRI scanning, eye position will be monitored using a MR-compatible eye tracking device that is mounted on the MR head coil and will not pose any discomfort to the participant. Depending on the experiment, subjects will either maintain fixation or track visual stimuli as they are presented on a computer screen. Eye-tracking data such as scan path and number/duration of fixations, and pupil diameter will be recorded during presentation of stimuli.

Face and body monitoring:

In some experiments we may track position and movement of a subject's body or parts of the body such as the face and hands, by using sensors and other tracking devices such as a video camera. These position and movement data will be used to interpret behavioral, fMRI, MEG or EEG data.

Physiological monitoring:

In some cognitive experiments we may use additional pieces of equipment for physiological monitoring. For example, in studies of emotional perception, we may use skin conductance equipment to measure the galvanic skin response. This is done by applying adhesive sensors and conductive gels to the subjects' fingertips.

When performing fMRI, MEG and EEG studies of the brain, one frequently needs or wants physiological information relating to how well the brain responds to sensory motor or visual stimulation. Non-invasive physiological monitoring devices including electrocardiogram, oxygen saturation monitor, end tidal carbon-dioxide (CO₂) monitor, noninvasive blood pressure monitor, galvanic skin response, skin temperature and capnometer may be used during the MRI, MEG and EEG data acquisition. For example, we may record physiological parameters such as the cardiac cycle using a finger ECG monitor, and respiration rate using a respiration belt around the abdomen. The observed physiological signals will be used for assisting interpretation of

fMRI, EEG and MEG data and for correction of interferences caused by physiological fluctuations.

Electrical Shock:

In some cognitive experiments, we may use electrical shock as a stimulus to elicit an emotional or anxious response. This is done by first cleaning the skin of the ankle, foot, hand or wrist with a mildly abrasive paste and then applying small metal electrodes. Before the session, subjects will experience the shock and select a level of shock that is unpleasant but not painful based on their evaluation. A few sample shocks will be given and subjects will be asked how strongly they feel them. During the experiment itself, shocks may be given on some or all the trials. The BIOPAC MP150 system (or similar) with stimulation modules (such as STM100C and STMISOC) will be used to deliver the shock. The intensity of the shock will be tailored to each individual subject to be unpleasant but not painful and will range between 0.1 to 5 mA.

Gustatory Stimulus Delivery:

Some behavioral, MEG, EEG, or fMRI studies of how we process food-related stimuli will be accompanied by gustatory stimulus delivery. This involves the delivery of small amounts of liquid directly onto a subject's tongue, using our NIH custom-built tastant-delivery system. Subjects may either sit or lie supine during stimulus delivery, and will receive a sweet, bitter, salty, sour, or savory tastant, or a tasteless (neutral) solution during testing. Each tastant will be made in solutions of varying concentrations. All tastants will be prepared in NIH approved facilities. The neutral solution will also be used as a "wash", to rinse out subjects' mouths between different tastants. Each "sweet", "sour", "salty", "bitter", "savory", or "neutral" tastant delivery will consist of 0.4 – 1.2mL of liquid (equal to 1/12 – 1/4 of a teaspoon).

Tastants will be delivered to the subjects' mouths by our specially built computer-controlled, MR-compatible, pneumatic-pressurized tastant-delivery system. Liquids are released downwards from syringes through latex-free hospital-grade plastic tubing into a gustatory manifold attached to the head coil and adjusted to fit into the subject's mouth. This tastant delivery system has been used in multiple previous studies of gustatory perception (see Simmons et al. 2013; Avery et al. 2015, 2017, & 2018). Over the past several years we have successfully completed these studies in 90 subjects using this equipment under NIMH protocol 10-M-0027 and NIDDK protocol 09-DK-0081, without incident.

Task Descriptions:

All tasks have been sub-divided into 7 themes as follows. All experimental tasks are for research purposes only.

A. Attention (4 experiments)

i. What are the cortical regions involved in endogenous and exogenous visual attention?(Ungerleider)

Experimental Procedures:

In this experiment participants will perform an orientation discrimination task, while viewing stimuli on a computer screen and making responses using a button device. Trials will comprise a cue that either predicts the location of a subsequent stimulus (endogenous attention condition) or is unrelated to it (exogenous attention condition). A variable amount of time (range 0 to 1 s) will separate the cue from the stimulus temporally. The subsequent stimulus will be a tilted low contrast grating (a Gabor patch; Liu et al., 2005) and subjects will be required to press a button to

indicate the direction of orientation of the grating. On some other control trials, only the stimulus will be presented such that it will not be preceded by a cue.

Subsequent to the behavioral experiment a separate fMRI session (not to exceed 2 hours) will be scheduled for each subject. Data from the fMRI experiment will help to identify the different regions in the dorsal and ventral fronto-parietal networks that are involved in the task.

Outcome Measures:

Outcome measures for this study will be reaction times and accuracy on the behavioral task and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox et al 1996). Correlations between behavioral measures and brain activity will also be computed.

ii. Spatial selectivity in the exogenous attention system (Ungerleider)

Experimental Procedures:

Two experiments will be conducted. In Experiment 1, stimuli will be one of six adjacent wedge-shaped texture patterns presented on a grayscale background. The texture will be an array of black dots whose radii increase rapidly, so as to create the appearance of approaching the observer. This dynamic texture has several virtues. First, briefly presented, expanding circles are known to elicit exogenous attention. Second, the texture's presentation will not produce an afterimage. Third, unlike the timeframe of a more traditional radial checkerboard texture, the short frame duration will permit each expanding dot stimulus presentation to be completed in only 132 ms, which is not enough time to make a saccade. Thus, even if a subject breaks fixation when a wedge appears, the wedge will not be present when the eye movement is completed. Each wedge will be within either the left or right visual field and will be presented one at a time, with an average interval of 11.25 seconds between presentation onsets. In Experiment 2: Stimuli will be one of four adjacent, concentric ring-shaped texture patterns presented on a grayscale background. The rings will be of uniform width. The set of all four rings cover the same circular portion of the visual field that is covered by the set of all six wedges used in Experiment 1. The texture will be the same expanding dot array used in Experiment 1. The rings will be presented one at a time, with an average interval of 11.5 seconds between presentation onsets.

Outcome Measures:

Our primary outcome measure will be the percent correct predictions by MVPA in the regions of interest (ROIs) defined by positive activations to the stimuli. The data from Experiment 1 will be used to identify ROIs for MVPA analysis of the Experiment 2 data, and vice versa.

Analysis procedures:

Standard MVPA and support vector machine (SVM) analysis methods will be used to analyze the data in these two experiments.

iii. What is the role of attention in perceptual learning? (Ungerleider)

Experimental Procedures:

In this study we will have two separate groups of subjects: experimental and control groups. For subjects in the experimental group we will measure the contrast thresholds at four training locations in the visual field in several behavioral sessions. These subjects will be scanned before and after four days of training. In a separate scan session, we will acquire their retinotopic mapping data. Subjects in the control group will undergo contrast threshold measurement and

fMRI scan sessions as well, but without training. The subject's task during contrast threshold measurements and training will be an orientation discrimination of a Gabor patch, whereas during fMRI scan sessions it will be color change detection at the fixation spot in the middle of a screen while a Gabor patch at the training locations is presented as a task-irrelevant stimulus. The experimental procedure for behavioral data acquisition will be the same as the methods used in Mukai et al. (2011): for contrast threshold measurements we will use a staircase method, in which contrast will be reduced after three correct responses and will be increased after one incorrect response, and during training we will have experimental subjects allocate three different levels of exogenous attention (attended, divided-attended and unattended) to different stimulus locations. During two pre- and post-training fMRI scan sessions, we will present a Gabor patch or flickering colored checkerboard (stimulus localizer scan) at four training locations at a time in a block design. In a separate fMRI session, we will obtain retinotopic mapping data by presenting a clockwise/counterclockwise rotating wedge and expanding/contracting rings. Subject's task will be to report via button press a change in color of fixation.

Outcome Measures:

Outcome measures for this study will be contrast thresholds at each training location, accuracy and reaction time for correct trials on the orientation discrimination task during training, and %BOLD signal change obtained pre- and post-training.

Analysis Procedures:

Behavioral and fMRI data will be processed and analyzed via standard procedures. In addition, for the fMRI data, we will define ROIs in the early visual areas corresponding to four stimulus locations based on retinotopic maps and localizer data, and compared the data from two scan sessions. The retinotopic maps will be obtained by estimating the time delay between each voxel time series and a reference time series. We expect to find strong correlation between perceptual learning changes in brain activations in the corresponding early visual areas.

iv. How do covertly observed fluctuations in sustained attention – and neurofeedback of these fluctuations – map from brain to behavior? (Bandettini)

Experimental Procedures:

Subjects will perform various behavioral tasks – such as reading, watching a video, playing a game, resting, or responding to various visual or auditory stimuli with a button press – during which their minds may wander. During some blocks, they may be instructed to focus acutely or to let their minds wander freely. To increase subjects' motivation to attend more closely during certain blocks of trials, they may be offered additional monetary rewards of up to \$20 for good performance. Their attention to the task will be measured periodically by testing their memory of the task or presenting “thought probes” that allow subjects to specify their current level of attention (Smallwood & Schooler, 2006). As they perform the tasks, we will record behavioral, fMRI, eye tracking, and/or other physiological data. We will use the data to build a classifier that can distinguish moments when a subject is maintaining attention on the task at hand from moments when his/her mind is wandering. These predictions may be verified through post-hoc analysis of behavior, or by using real-time AFNI software to detect the signals of interest and trigger thought probes. Subjects may be given questionnaires about their propensity for mind-wandering in daily life; this will help investigate differences between subjects in the level of sustained attention. The real-time detection of mind-wandering may also be used to give feedback to the subject in an attempt to manipulate his/her level of attention. For example, we might remind the subject to focus, give the subject a quiz, or change the presentation style.

Because training an effective classifier may require a great deal of data and time, the subject may be asked to come back for more than one session.

Outcome Measures:

Outcome measures for this study will be reaction times and accuracy on the behavioral tasks, answers to the thought probes, recall tests, and questionnaires, and the output of the classifier.

Analysis Procedures:

The analysis procedures described in the “Multivariate Analysis fMRI experiments” section will be applied to build a classifier based on the BOLD signal from grey matter or a selected ROI. In addition, we may include non-BOLD features such as pupil dilation, saccade frequency, or heart rate as inputs to the classifier. Assessment of the classifier will be based on the level of agreement between the classifier output and overt measures of sustained attention inferred from behavioral responses, thought probes, recall tests, and/or questionnaires.

B. Decision-making (12 experiments)

i. *What are the brain regions whose activity predicts individual differences in the use of prior knowledge during decision-making? (Ungerleider) (COMPLETED)*

Experimental Procedures:

In this experiment, subjects will view target stimuli that will be circles distorted by a sinusoidal modulation ranging linearly from 4% to 22% of the mean radius. During scanning, the targets will be presented on a screen one at a time with random sizes, orientations and locations to prevent subjects from relying on retinotopic location or spatial attention in order to perform well. The task will be to decide whether each target is bumpy or smooth, with the smoothest target defined as the Category S prototype and the bumpiest as the Category B prototype. Distributions of Category S and B shapes will be integer approximations of overlapping Gaussians. A cue presented before each target will be “80/20” in half the runs, indicating an 80% and 20% chance that the upcoming target will be of Category S (or B) respectively. The cue in the other runs will be “50/50”, indicating equal chance that the upcoming target will be of category S and B.

Outcome measures:

Our primary outcome measure will be the extent to which activity changes in each voxel and subject, correlates with the extent of the bias shift across subjects. As we will use an event-related design, we can extract the fMRI response on each trial.

Analysis procedures:

We will calculate the behavioral decision criterion for each subject using the subject’s button press data and standard signal detection methods. We will use multiple regression to identify beta weights representing the percent signal change vs. baseline attributable to report change trials, the specific trial set driving the decision criterion shift predicted to occur across the cue conditions. The differences between the beta weights from 80/20 runs vs. 50/50 runs for each subject will be used as inputs to a second multiple regression analysis, calculating voxel-wise correlations between the size of the behavioral bias shift across prior knowledge cue conditions and the size of the fMR signal change across prior knowledge cue conditions during the report change trials. From the correlation results, clusters passing a size cutoff for statistical significance will be identified.

ii. *Perception vs. judgment: Are there stimulus specific effects of prior knowledge on decision-making? (Ungerleider) (COMPLETED)*

Experimental Procedures:

Target stimuli will be circles distorted by a sinusoidal modulation. In the perceptual uncertainty condition, the targets will be degraded with noise. In the categorical uncertainty condition, the targets will be very similar to one another. During scanning, the targets will be presented one at a time with random sizes, orientations and locations to prevent subjects from relying on retinotopic location or spatial attention in order to perform well. The task will be to decide whether each target is from Category S or Category B, with the smoothest target defined as the Category S prototype and the bumpiest as the Category B prototype. For some subjects, a cue presented before each target will be “80/20”, indicating an 80% and 20% chance that the upcoming target will be of Category S (or B) respectively. These subjects will receive an 80/20 distribution of targets in pre-scanning training. Other subjects will receive a sham cue of “OO/OO” indicating no prior information about the target distributions. These subjects will receive a 50/50 distribution of targets in pre-scanning training. To control for stimulus-level confound, all subjects will receive identical 50/50 distributions of targets during scanning.

Outcome measures:

Our primary outcome measure will be the difference in activation between the perceptual and the categorical uncertainty conditions, pooled across all subjects. These data will be used to identify regions of interest (ROIs). We will then examine the within-ROI data from each subject group (prior knowledge and naïve) separately to determine whether activation differences are attributable to prior knowledge.

Analysis procedures:

We will use multiple regression to identify beta weights representing the percent signal change vs. baseline attributable to decisions under perceptual and categorical uncertainty respectively, pooled across all subjects. Clusters of differences between the perceptual vs. categorical uncertainty beta weights that pass a size cutoff for statistical significance will identify ROIs. In each ROI, we will plot activity levels for the prior knowledge and the naïve subjects separately to determine whether the prior knowledge accounts for the activation differences.

iii. What is the role of reward in perceptual decision-making? (Ungerleider)

Experimental Procedures:

Subjects will participate in an fMRI study involving categorization of noise-degraded images of faces and houses. Four levels of noise: 46%, 54%, 56% and 58% will be used for degradation of images. To study the effect of incentive, four reward levels will be used: No Reward, Equal Reward, High Face Reward (higher reward for correct face than house), and High House Reward (higher reward for correct house than face). On No Reward trials, subjects will receive simple feedback, i.e., correct or incorrect. On Equal Reward trials, subjects will win 10¢ for a correct face or house response. On High Face Reward trials, subjects will win 20¢ for a correct face response and 10¢ for a correct house response. On High House Reward trials, subjects will win 20¢ for a correct house response and 10¢ for a correct face response. All incorrect responses will result in a loss of 2¢ while missed or late responses will result in a loss of 5¢. On each trial, prior to stimulus presentation, subjects will be cued to the level of reward for the upcoming trial. Each fMRI experiment will last no more than 2 hours. A few days prior to the fMRI session, subjects will be asked to come in for a one hour behavioral session for calibration purposes. At the end of each session, subjects will be paid the amount that they won during the session, in addition to the regular compensation for the experimental session.

Outcome Measures:

Our primary outcome measure will be change in brain activation levels with different levels of reward. Other outcome measures will be decision criterion and reaction time on task.

Analysis Procedures:

Behavioral data will be analyzed to obtain mean reaction time and accuracy values. Further, signal detection theory will be used to estimate each subject's decision criterion and d-prime values. fMRI data will be preprocessed and analyzed using standard fMRI methods.

iv. How do simultaneous changes in perceptual and reward uncertainty impact neural dynamics and decision-making? (Ungerleider)

Experimental Procedures:

Overview: Participants will be invited to complete decision-making tasks where they may detect and choose between multiple stimuli to earn a probabilistic reward. Stimuli may include neutral faces, houses, cars or other objects selected from publicly available stimulus sets. Participants will be instructed to make choices to maximize reward. To study the effect of manipulations in both perceptual and reward uncertainty on decision-making behavior and associated neural activity, participants may be shown four stimuli on each trial (1 face, 1 house (targets), 2 cars (distractors). Targets may be shown at multiple levels of visual coherence (exact levels will be determined based on behavioral piloting). To allow the possibility for the subject to make errors and decrease the predictability of the perceptual and reward outcomes, distractor stimuli may always be presented at the lowest level of coherence and its selection may never result in any reward. Participants may be asked to make speeded choices and will be rewarded probabilistically based on their choice. The probability of receiving two possible reward outcomes (e.g. win 8¢ (high reward) or win 2¢ (low reward)) based on which target is selected may also be manipulated across multiple levels. The exact values may change based on behavioral piloting to maximize discriminability between these levels (e.g. 10¢ and 0¢; or win 8¢ or lose 2¢). If participants do not respond within the allotted time frame, they may receive no reward. Participants may be informed of these contingencies. They may also be shown a cue that signals the outcome likelihood and degree of noise for each target stimulus. Alternatively, the task may require learning of these contingencies based on choices and feedback. Trials may be followed by feedback about the target selected and its associated outcome.

Two versions of the task will be used and both may be administered behaviorally and/or while undergoing fMRI. The first version of the task will have fixed reward-probabilities for each target within each block (varied probabilities between blocks), but will vary perceptual uncertainty between targets on a trial-by-trial basis. The second version of the task will include fixed perceptual uncertainty within block (varied between blocks), and will vary reward probabilities between targets on a trial-by-trial basis. Recent work has shown that the frequency at which reward uncertainty is manipulated can alter decision behavior and underlying neural correlates (Payzan-Lenestour & Bossaerts, 2011; Payzan-LeNestour, Dunne, Bossaerts, & O'Doherty, 2013). Given our question of interest, these two proposed versions of the task will allow us to test for changes in neural substrates as a function of manipulations in: a) perceptual or reward information; and b) the frequency of change in perceptual or reward information.

The specific number of perceptual and reward uncertainty conditions and number of scanning sessions required will be determined following behavioral piloting. It is estimated that participants may be required to complete two fMRI sessions. To appropriately measure changes in neural response to the different reward conditions and motivate naturalistic behavior, we may pay participants a proportion of the money they earn during the task in addition to regular compensation for the experimental sessions (proportion determined during behavioral piloting).

We may also obtain basic physiological measures such as respiration and heart rate to account for noise in BOLD signal due to physiological changes and as a measure of arousal and reactivity.

Participants may also be asked to attend a separate session to complete a battery of self-report and neuropsychological/cognitive tasks (see Section 4-e: Neuropsychological Testing and Questionnaires). Participants may be provided with a print or email packet of self-report measures to complete during a visit or to complete at home. These measures may also be administered via other means (example the NIH Clinical Trial Database Website, Qualtrics, Inquisit, etc.). These measures will aid in understanding how individual differences across related cognitive and affective domains are associated with decision-making behavior and perceptual and reward-uncertainty manipulations.

Outcome Measures:

Primary outcome measures will include changes in fMRI brain activation due to perceptual and reward manipulations, behavioral performance on the task, reaction times, performance on neuropsychological/cognitive testing, and scores on self-report measures.

Analysis Procedures:

Behavioral and neural data will be modeled using computational models of decision-making based on predictive coding, sequential sampling, and economic theories. We may use machine learning, univariate, and multivariate approaches to uncover changes in behavior, neural activity, and functional connectivity as a function of manipulations in perceptual and reward uncertainty. We may also use these methods to test how task version 1 and 2 manipulations impact the interactions between perceptual and reward information in decision-making, as well as how manipulations of interest relate to individual differences in basic cognitive and affective domains.

v. *Effects of perceived animacy on neural mechanisms of decision-making (Martin)*

Experimental Procedure:

Our study will combine a motion direction discrimination paradigm using control stimuli (plain white dots) and “minimalist” animate stimuli (i.e., white dots with two smaller red dots, Gao et al., 2010) with an extended reveal fMRI paradigm that can be used to generate more precise processing descriptions than conventional fMRI designs. In this paradigm, increasingly high-quality (i.e., less noisy) sensory information is revealed over the course of multiple MR volume acquisitions. Trials are binned for analysis based on subjects’ response time, which will enable us to distinguish brain regions involved in *sensory processing*, *accumulating evidence* for decisions, and *decision/response selection*. Critically, task demands and patterns of motion will be matched across stimuli, and subjects will be told that there is no relationship between the position of the red dots and the direction of motion for the experimental stimulus. This design will allow us to test whether minimalist stimuli presented in non-social contexts automatically recruit brain regions important for animacy inference.

During each scanning session, participants will be asked to determine the direction of motion for a set of dots (either control or animate). Stimuli will appear on the screen for 6 s. The stimulus will be followed by a 2-10 s fixation period where subjects will view a fixation crosshair and await the start of the next trial. Resting-state data will be acquired before and after the task runs to determine how the functional connectivity of spontaneous BOLD signal fluctuations in different brain regions, computed with correlation coefficients, relates to task performance.

Outcome measures:

Our two primary measures will be: 1) BOLD signal collected while participants view and make decisions about control or animate stimuli and 2) BOLD signal collected while subjects rest in the scanner. Additional measures will be reaction time and accuracy of response on each trial.

Analysis procedure:

Single-subject data (first-level) will be binned based on subjects' response time for control and animate motion. Single-subject data will be carried forward for a group (second-level) analysis designed to identify regions of interest (ROIs) modulated during task performance with a Motion Type (control vs. animate) x Response Bin (1,2,3) X Timepoint (0-18 s) ANOVA. Three properties of ROIs' BOLD signals (i.e., onset point, time of peak, and full-width and half maximum) will be analyzed to distinguish "sensory", "accumulator", and "decision/response selection" regions. ROIs identified from the task-analysis will be used as seed ROIs for resting-state functional connectivity MRI (fcMRI) analyses. The degree of correlation in spontaneous BOLD signal fluctuations between ROI pairs will be computed.

vi. *Do humans learn category assignments more quickly in asymmetrical reinforcement conditions? (Leopold)*

Experimental Procedures:

The experiment will involve behavioral testing, where subjects view a sequence of images. In the symmetrical condition, they will be instructed to press one of two equivalent keys (category A and category B) following each image presentation. For each image, a correct response (button A or button B) will be followed by positive feedback (green screen) and the incorrect response by negative feedback (red screen). In the asymmetrical condition, the stimuli are still divided into categories A and B but only category A is positively reinforced. The two response keys will thus have different meanings ("Hit_A" and "Pass"). Subjects are instructed to press the "Hit_A" button when they believe the stimulus is of category A, whereas they can press the Pass button when they believe the stimulus is not of category A. Pressing the "Hit_A" button when the category is B will result in an undesirable delay.

Outcome Measures:

Our primary outcome measure will be the difference between learning rates and reaction times between the two learning conditions.

Analysis Procedures:

Behavioral data will be analyzed to obtain mean learning rates and reaction times. Analysis will be performed using custom written MATLAB code to plot differences between symmetrical and asymmetrical conditions.

vii. *What is the role of the ventromedial prefrontal cortex (VMPFC) in encoding expected reinforcement outcomes during decision-making? (Blair)*

Experimental Procedures:

In this study participants will be presented with single stimuli and asked to choose whether to respond to them or not. Responding to "good" stimuli will engender reward (point gain) while responding to "bad" stimuli will engender punishment (point loss). By examining the response to the choice of the different objects as a function of learning, it is possible to determine which regions are involved in the representation of reinforcement value during passive avoidance learning.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

viii. *The selection of response options on the basis of reinforcement expectancies: the impact of inter-object reinforcement distance (Blair)*

Experimental Procedures:

In this study participants will be presented with choices between two different objects. Each object (there will be 10) will be associated with a different reinforcement level (i.e., choice of object A wins 100 points, choice of object B, 300 points). By examining the response to the reinforcement value of the object chosen it is possible to determine which regions are involved in the representation of reinforcement value. By examining the response to the inter-object reinforcement distance (in the case above, the distance between A and B would be 200. However, if the choice was between A and C, worth 500 points, the distance would be 400), it is possible to determine which regions are involved in responding to decision conflict.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

ix. *The selection of response options on the basis of reinforcement expectancies: the impact of number of response options (Blair)*

Experimental Procedures:

In this study participants will be presented with choices between two, three or four different objects. Each object will be associated with a different reinforcement level (i.e., choice of object A wins 100 points, choice of object B, 300 points). By examining the response to the reinforcement value of the object chosen it is possible to determine which regions are involved in the representation of reinforcement value. By examining the response to the number of response options available (four as opposed to two, for example), it is possible to determine which regions are involved in responding to decision conflict.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

x. What are the functional roles of ventromedial, dorsomedial and inferior frontal cortices during reversal learning? (Blair)

Experimental Procedures:

In this study, participants will be presented with choices between two stimuli. Responding to one of these stimuli will be more likely to engender reward (80% probability) than punishment (20% probability). Responding to the other stimuli will be more likely to engender punishment than reward (the contingencies are opposite). After a set number of trials the reinforcement contingencies change such that the previously “good” stimulus is now more likely to engender punishment and the previously “bad” stimulus is now more likely to engender reward.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

xi. What is the functional role of ventromedial frontal cortex during operant extinction? (Blair)

Experimental Procedures:

In this study, participants will be presented with single stimuli and asked to choose whether to respond to them or not. Responding to “good” stimuli will engender reward (point gain) while responding to “bad” stimuli will engender punishment (point loss). After a set number of trials, 50% of the “good” stimuli will become “bad” and responding to them will engender punishment. In addition, 50% of the “bad” stimuli will become “good” and responding to them will now engender reward. By examining the neural response to successful extinction it is possible to determine which neural systems are important for this form of extinction.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

xii. What is the neural basis of the optimistic bias? (Blair)

Experimental Procedures:

In this study participants will be presented with possible positive and negative future events in the scanner and asked to estimate the probability that these might occur to them. The participants will indicate their likelihood using a four-point scale.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and

analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

C. Emotion processing (7 experiments)

i. Variability in Fearful Face Processing in Healthy Individuals using prior probability (Ungerleider)

Experimental Procedures:

The fMRI experiment will consist of 9 runs – 3 runs with 80% fear faces and 20% neutral faces (fear expected, neutral unexpected), 3 runs with 20% fear faces and 80% neutral faces (neutral expected, fear unexpected), and 3 runs with 50% fear faces and 50% neutral faces (uncertain expectancy for all faces). Each run will contain 50 trials – each trial will include a 4 second anticipation period (triggered by a red fixation cross cue for 250 ms) and a response period (beginning with the 250 ms presentation of the face). Subjects will receive explicit knowledge prior to the start of a run as to which expectation condition will follow (80F:20N, 20F:80N, or 50F:50N). Subjects will be instructed to respond as fast and as accurately as possible to whether they had just seen a fearful or neutral face by pressing one of two buttons. Prior to entering the scanner all subjects will complete the Spielberger State Trait Anxiety Inventory (Spielberger and Gorsuch, 1983), NEO Five Factor Inventory (Costa and McCrae, 1992), and Tridimensional Personality Questionnaire on Harm Avoidance (Cloninger et al., 1991).

Outcome Measures:

Outcome measures for this experiment will be reaction times on the task, and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures, personality measures and brain activity will be computed.

ii. Facial expression and identity processing investigated using multi-voxel pattern analysis methods (Ungerleider)

Experimental Procedures:

Subjects will be scanned while viewing pictures of facial expression and asked to perform a fixation color discriminate task. On each trial, subjects will be shown a face image for 300 ms. Face pictures depicting angry, sad, afraid, happy, surprise, disgusting or neutral expressions will be used. Further, different facial identities depicting each of these expressions will be used.

Outcome Measures:

fMRI percent signal change in response to the different facial expressions and identities will be the primary outcome measure.

Analysis Procedures:

Besides the standard GLM univariate analysis methods, multivariate pattern analyses (MVPA) will be applied to the fMRI data. Voxels chosen for analysis will be from the amygdala, FFA, occipital face area (OFA), STS and additional regions, if necessary. Linear support vector machine (SVM) methods will be used to train a classifier to discriminate between the pattern of activity for different expressions and identities.

iii. The temporal dynamics of the response to fearful expressions (Blair)

Experimental Procedures:

In this MEG study, participants will respond by button press regarding the gender of faces. Half of these faces will be neutral, the other half fearful.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and change in gamma band power in the MEG experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. Gamma band data will be preprocessed and analyzed using standard procedures. Correlations between behavioral measures and brain MEG activity will also be computed.

iv. The impact of processing load on the response to emotional expressions (Blair)

Experimental Procedures:

In this study, participants will respond by button press to stimuli under three conditions judging: (i) the gender of the displayed expression; or (ii) the case (Upper or lower) of a word superimposed on the face; or (iii) the number of syllables (one or two) of a word superimposed on the face. Faces will either display neutral or fearful affect.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

v. The impact of processing load on the response to environmental threats and appetitive stimuli (Blair)

Experimental Procedures:

In this study, participants will be exposed to three types of trial: (i) view trials (where only a visual image is displayed); (ii) congruent trials (where images temporally bracket a numerical array that is congruent; i.e., two 2s); and (iii) incongruent trials (where images bracket a numerical array that is incongruent; i.e., three 2s). For view trials, no response is required. However, for congruent and incongruent trials participants are required to respond, via button press, according to how many Arabic numerals are presented on the screen. Congruent trials require less recruitment of top-down attentional control systems than incongruent trials (Kerns et al., 2004). Within a trial, the array of stimuli is: image (400ms), numerical array (400ms – this is blank for view trials), image (400ms), interstimulus interval (1000ms). The participant can respond at any point after the number array is presented. The images will be either negative, positive or neutral and taken from the IAPS picture set.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and

analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

vi. *The impact of emotional distracters on the recruitment of systems involved in top-down attentional control (Blair)*

Experimental Procedures:

In this study, participants will be exposed to two types of trial: (i) task trials (where no emotional distracters are present); and (ii) distracter trials (where images temporally bracket the task stimulus). The participant's task is to respond, via button press, to two different shapes. Within a trial, the array of stimuli is: image (400ms), task stimulus (250ms), image (400ms), interstimulus interval (1000ms). The participant can respond at any point after the task stimulus is presented. The images will either be negative, positive or neutral, taken from the IAPS picture set.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

vii. *Neural circuits for representing threat and illness (Martin)*

Experimental Procedures:

In this fMRI experiment, subjects will view pictures of objects and scenes and be asked to press a button whenever a picture repeats (one-back task). Threatening stimuli will consist of pictures judged to be threatening (e.g. pictures of guns, knives, dental drills and scenes of violent such as one would see in major newspapers and magazines). Images used will be similar to those present in the International Affective Picture System (IAPS), a well-known and often used visual stimuli set. Illness stimuli will be pictures of persons with visible signs of illness e.g. sneezing, coughing, signs of fever or general malaise not unlike pictures in the media or in advertising. Prior to scanning, stimulus sets will be equated on affective valence and arousal by obtaining independent ratings using 7-point rating scales. Control stimuli will include pictures of appetizing foods and common objects from our previous fMRI studies (Simmons et al., 2005).

Outcome Measures:

Outcome measures for this study will be reaction times to detect repeated stimuli and percent signal change in the fMRI experiment.

Analysis Procedures:

Differences in BOLD fMRI activity will be analyzed using repeated measures random effects models. The statistical maps will be thresholded at $q(\text{FDR}) < 0.05$, using the false discovery rate (FDR) approach for multiple comparisons correction. MRI and behavioral data may also be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

D. Perception (19 experiments)

i. Is the contribution of the dorsal visual stream to shape perception tuned to tool-like objects or does it respond similarly to multiple object categories? (Ungerleider)

Experimental Procedures:

Participants will be presented with images comprising two panels, one to the left and one to the right of the screen center. The two objects shown will always depict the same object category (for example, two office chairs) but can differ between panels with respect to shape (e.g., two slightly different office chairs) or location (e.g., closer or further relative to the line) but not both. Object images will be acquired from (<http://tarrlab.cnbc.cmu.edu/>) including tools and common everyday objects/items that do not belong in the tool category and do not have a distinct hand motor-action associated with them (ex. airplane). On each trial, participants will be required to press a button if the two panels are different (in either shape or location) or withhold response if the panels are the same.

Localizer tasks. Prior to completing the main task, participants will complete two localizer tasks: A shape localizer and a location localizer task. During the shape localizer task, participants will view two images of either whole or phase-scrambled, everyday household objects displayed on either side of the screen center and decide if they are the same or different. On each trial of the location localizer task, participants will view a display with two panels containing a dot and a line, shown to either side of the screen center. The task of the participants will be to decide if the distance between the dot and line in each panel is the same or different.

Outcome Measures:

Outcome measures for this study will be reaction times and accuracy for the behavioral task, percent signal change in the fMRI experiment and signal amplitude in the MEG experiment.

Analysis Procedures:

Activity in response to Task type and Object category will be explored with repeated measures random effects models (RFX GLM; separate analyses will be performed for each localized ROI). The statistical maps resulting from the RFX analyses will be thresholded at $q(\text{FDR}) < 0.05$, using the false discovery rate approach for multiple comparisons correction (Genovese, Lazar & Nichols, 2002).

ii. Is shape processing in the dorsal visual stream comparable to shape processing in the ventral visual stream? (Ungerleider)

Experimental Procedures:

This experiment will include a behavioral session as well as an fMRI session. The experimental procedure will be identical to that the previous experiment, but with shape differences will be replaced with two types of texture differences: *texture type* and *texture location*. The experiment will comprise two parts. At the beginning of each section participants will be given a rule, written and spoken, instructing them to search for location differences only (Rlocation) in Part 1 and for any type of texture difference (Rtexture) in Part 2, with Rlocation always preceding Rtexture. Each block will include trials with scene-based location differences, no differences and one type of texture difference (either texture type or texture location depending on the block). In each trial, participants will be required to indicate with a button press if the two panels have the same or different target attribute. The fMRI session will be similar to the behavioral session, except that it will follow a fast event-related design with the three types of trials described above. On each trial, participants will be required to identify texture type differences or texture location differences. Participants will be asked to withhold response during identical trials.

Localizer tasks. Prior to completing the main task, participants will complete the localizer tasks described in the previous experiment.

Outcome Measures:

RT and accuracy data on the task, and fMRI percent signal change on different task conditions will be the measures of interest.

Analysis Procedures:

Behavioral data will be analyzed to obtain mean reaction time and accuracy values for each type of trial under each rule. Activity in response to Trial Type will be explored with repeated measures random effects models (RFX GLM). Separate analyses will be performed for each localized region of interest (ROI). The statistical maps resulting from the RFX analyses will be thresholded at $q(\text{FDR}) < 0.05$, using the false discovery rate approach for multiple comparisons correction (Genovese, Lazar & Nichols, 2002).

iii. *Inhibition between face and house processing in the ventral stream (Ungerleider)*

Experimental Procedures:

The experimental hypothesis is that FFA will show a smaller response to fast event-related presentation of [scenes + faces] compared to [faces + faces], and [face images + scrambled images]. Similarly, PPA will show a smaller response to [faces + scenes] compared to [scenes + scenes] and [scrambled + scenes]. Such a finding would support the hypothesis of neural inhibition between these two functionally distinct ‘streams’.

In this jittered fast event-related fMRI experiment, subjects will view two images sequentially and briefly displayed on the screen. For instance, the two images could be face + scene, scene + face, face + face, scene + scene, scrambled (matched to scene statistics) + face, scrambled (matched to faces statistics) + scene. Subjects will be instructed to categorize the second image in each pair as either male, female, indoor scene, or outdoor scene by pressing a key corresponding to that category - while ignoring the first image.

Outcome Measures:

We will measure subjects’ behavioral performance (error rate, and reaction time), and fMRI BOLD percent signal change during the scanning.

Analysis Procedures:

The fMRI data will be processed with FsFast (FreeSurfer function analysis stream) with standard preprocessing parameters, such as motion correction, slice time correction, spatial smoothing. Then, a FIR (finite impulse response) analysis will be used to extract the shape of the BOLD response. The peak of the BOLD time course will be used to compare between conditions. Behavioral data will be analyzed with customized MATLAB programs.

iv. *Curvature: a crucial dimension for face processing (Ungerleider)*

Experimental Procedures:

Behavioral task: Stimuli include computer generated faces and high-pass filtered chairs. In each trial, a sample image (a face or chair) will be presented briefly, followed immediately by a mask to interrupt visual processing. The mask will then be followed by a 2-choice recognition test. Two kinds of masks will be used: noisy images with curved or straight elements. The presentation time of the sample images will vary from trial to trial using a staircase method to make performance comparable across conditions. This will yield a 2 X 2 design (faces vs. chairs and curved vs. straight masks). The curved masks will be generated by randomly placing curved patches (banana filters) across image space, which will be repeated three times using curved patches with different spatial frequencies. The straight masks will be generated in the

same way, except that the curved patches will be replaced by straight patches (Gabor patches). It is predicted that curved masks will impair the recognition of faces and straight masks will impair the recognition of chairs.

fMRI task: If the behavioral task yields positive results then it will be repeated in the fMRI scanner. Here, we will focus on activations in several regions-of-interest. For face recognition trials, we will analyze the occipital face area (OFA) (Gauthier et al., 2000), fusiform face area (FFA) (Kanwisher, McDermott, & Chun, 1997), and anterior temporal face area (ATFA) (Rajimehr et al, 2008). For chair recognition trials, we will analyze the lateral occipital complex (LOC) (Malach et al., 1995). For both behavioral and imaging experiments, participants will be free to stop testing at any time.

Outcome Measures:

We will measure subjects' behavioral performance (presentation times, error rate, and reaction time), and fMRI BOLD percent signal change during the scanning.

Behavioral outcome: We anticipate that participants will require significantly longer presentation times of the sample images to perform the face recognition task in the curved mask condition than in the straight mask condition; the converse is anticipated for the chair recognition task.

fMRI outcome: We anticipate that all face-selective regions will have reduced activation to faces in the curved mask condition than in the straight mask condition. Any difference in fMRI signal between OFA, FFA and ATFA might provide clues regarding the stage at which face processing is interrupted. Likewise, LOC is expected to have reduced activation to chairs in the straight mask condition than in the curved mask condition.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical method, such as two-way ANOVA. fMRI data will be analyzed using a variety of standard technique including univariate and multivariate approaches, as well as multiple-voxel pattern analyses.

v. *How do we understand other's actions? (Ungerleider)*

Experimental Procedures:

The project consists of three phases:

Phase 1: Body position tracking to generate naturalistic stimuli of human actions:

The main purpose of this phase is to record human body movements in naturalistic settings to generate the stimuli for the next two phases of the project. We believe that to generate naturalistic videos of human actions that could be later (in phase 2 & 3) used for the study of action goal and form reading, we need to measure the movements in interactive settings. To do this, we will recruit pairs of participants. One of the participants may be assigned the role of "actor" and the other may be assigned the role of "responder". We plan to attach motion tracking sensors to multiple body parts of the "actor" and record his/her movements while he/she performs movements in front of the "responder". The "responder" may be asked to read the actions of the "actor" and respond to them according to the task instructions. The role of the "responder" in this phase is to provide an interactive setting for the "actor" so that his/her recorded movements are as natural as possible. In addition to body position tracking, we may also record the movements of the "actor" with video recording cameras. We may then use the recorded body positions or videos to generate stimuli for experiments in phase 2 & 3. An example experiment is as follows: The "actor" and the "responder" sit in front of each other separated by a transparent screen. Two targets may be placed between them affixed to the screen. On each trial, the "actor" may be asked to reach for one of the two targets announced to him/her through headphones, and the "responder" will read the actions of the "actor" and reach for the same target as fast as he/she can (see Figure 1A for an example of the

experimental setup). The recorded body positions of the “actor” using sensors attached to the body (Figure 1B) may be used to generate point-light displays (Figure 1C) or stick-figures (similar to point-light displays but with connected lines, Figure 1D) of reach movements to the left and right targets. Note that in this phase of the project the form of the action is not separated from the goal of the action. The leftward movement always leads to the left target and the rightward movement always leads to the right target. We will dissociate the goal and form using the videos obtained from phase 1, later, in phases 2 and 3.

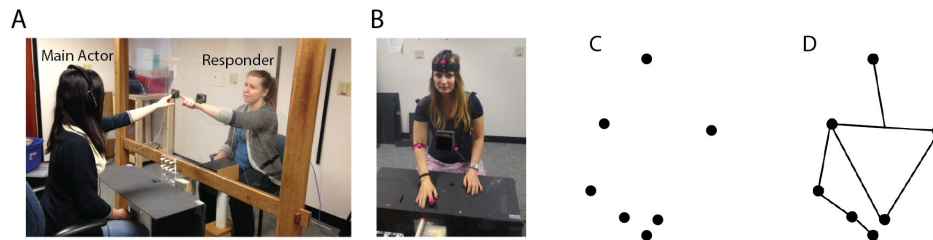


Figure 1: Examples of the A) experimental setup, B) a “actor” with sensors attached to the body, and C) point-light display, and D) stick-figures that will be generated using the motion tracking data from phase 1 and will be used in experiments of phases 2 and 3.

The finger position of the “responder” may also be recorded and analyzed to determine the reaction times and accuracies for action reading in naturalistic settings. We may change the task difficulty in this phase (for example by changing the distance between the two targets in the example above) to obtain action stimuli that are easier/harder to discriminate. The reaction times and accuracies of the responder may be useful as a measure of task difficulty. We may also analyze the recorded body positions of the “actor” to obtain an objective measure of when the direction of movement could be distinguished from the kinematics of the movements.

Body movements may be recorded using a motion tracking device (e.g., Polhemus Liberty <http://polhemus.com/motion-tracking/all-trackers/liberty>), a magnetic motion tracking system that records body positions with high spatiotemporal precision, as well as video recording cameras. The face of the participants may be visible in videos. Appropriate video release forms will be obtained from the participants, and the videos will only be used according to the release form (see Appendix 25H). The motion tracking data will only include the position of the body parts and will not include identifying information.

Variants of these proposed experiments have already been performed at Harvard University, and some videos have been obtained previously. We may use the videos and body tracking data collected at Harvard University for experiments described in phases 2 and 3. Harvard has agreed to share the data with NIMH, and a data use agreement is signed by both institutes. We will use the videos only according to the video release form obtained at the time of collecting the data at Harvard University.

Phase 2: Psychophysical experiments to separate action goal reading from action form reading:

In this phase, we will separate action goal and action from reading in psychophysical experiments. The videos and movement data collected in phase 1 will be used to generate the stimuli for this phase. Movement data/videos from phase 1 will be analyzed, cut to contain individual movements or parts of individual movements, and will be used to generate action stimuli containing point-light displays/stick-figures/video clips of movements (Figure 1C & D). In psychophysical experiments, the action stimuli will be modified so that the goal could be dissociated from the form. To dissociate the goal from the form of the movement in the reaching experiment described in phase 1, for example, we may present the stick-figure reaching actions either slightly to the left or slightly to the right side of the display. This way the actions will have two possible directions (left or right) and three possible goals (left, middle, and right). Figure 2 demonstrates snapshots of the example experimental conditions. Conditions A and B have the same goal but different forms. Conditions A and C, on the other hand, have the same form but different goals. Participants will then be presented with a series of these action stimuli on the computer screen and will be asked to perform a one-back repetition detection on either the goal or the form of the actions and will report their responses with button presses. The repetition detection task is preferred compared to a direct goal and form report as it will allow us to decouple the motor response (the button presses) from the action goal/form choices. This is important in the next phase of the experiment when we measure the fMRI responses in different experimental conditions.

The reaction times and accuracies will be analyzed to ascertain that the two tasks have equal difficulty levels. As control tasks, we may also ask participants to discriminate other

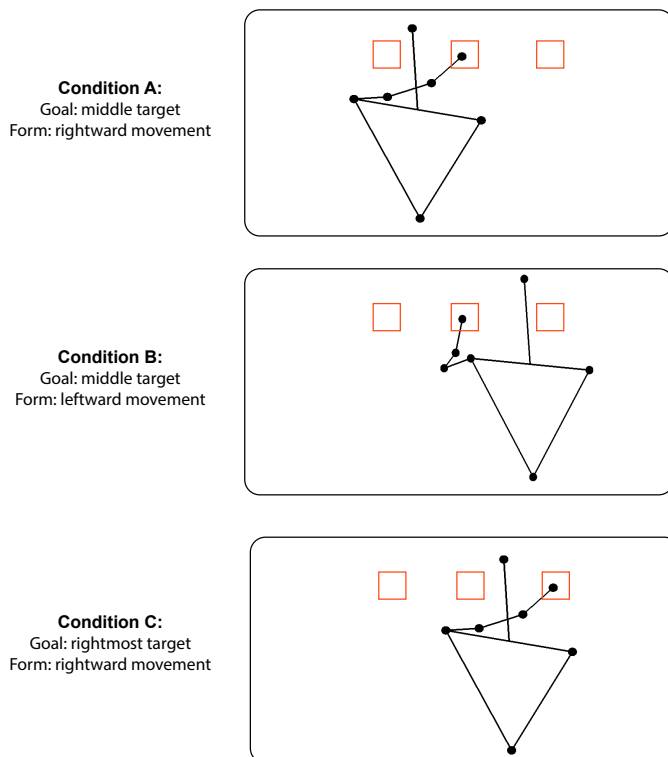


Figure 2: Three example experimental conditions for phases 2 and 3. The stick-figures are snapshots of the end point of actions. The squares show the three possible targets. Stick-figures are moved slightly to the left or right to dissociate action goal from action form. Conditions A and B have the same goal and different forms while conditions B and C have the same form and different goals.

attributes, such as the gender or identity of the actors in the stick-figure displays. In experiments of this phase of the project, the position of the eye may be recorded using an eye tracking system.

Phase 3: Functional MRI experiments:

The behavioral experiments in phase 2 will be used in phase 3 for functional MRI experiments. Participants may be asked to perform a one-back repetition detection task on either

the form or the goal of actions in the scanner. In these experiments, the position of the eye may be recorded using an eye tracking system. BOLD responses will be recorded and analyzed to determine the involvement of various brain regions in understanding the goal and the form of actions. Functional MRI experiments will be performed in single sessions (the number of sessions may increase depending on the pilot results). We may use a block-design paradigm that has high statistical power and allows us to measure the average BOLD response in each region during the goal and form discriminations tasks. We may also use an event-related paradigm that despite its lower statistical power will allow us to separate the BOLD response to individual stimulus and task combinations. This design allows us to use pattern classification techniques to measure the information content of each region for the form and goal of movement in each task. Each experimental session will last between 1.5-2 hours and may contain between 10-30 runs. Other than the main experimental runs, we may also include anatomical scan as well as localizer scan runs/sessions to identify regions of interest for each subject for the later analysis.

Outcome Measures:

Outcome measures for this study will be reaction time and accuracy of behavioral responses and fMRI brain activity.

Analysis Procedures:

The reaction times, accuracies, eye movement, and body movement measures will be analyzed using common statistical techniques. Functional MRI data will be analyzed using both univariate and multivariate techniques to determine differences in the average BOLD signal as well as differences in patterns of activity in each brain region across experimental conditions. We may also measure correlations between activity of different brain region to assess their functional connectivity.

vi. Laminar BOLD signal changes during perception versus mental imagery (Martin)

Experimental Procedures:

High-field (i.e., 7 Tesla) MRI will be used to acquire high-resolution (0.75 mm³) fMRI data. Subjects will perform two tasks, visual perception and mental imagery, on four stimulus categories, faces, places, animals, and tools. The regions in ventral temporal cortex that respond to these categories have been established. Thus, these stimuli will allow us to target a small swath of cortex to achieve our targeted spatial-resolution. During the visual perception task, participants will view pictures. During the mental imagery task, participants will view the names of items belonging to each category (e.g., hammer) and will try to form a clear, vivid mental image of the person, place, or thing. Subjects will press a button to indicate when they have viewed a picture or formed a mental image. Trials will be grouped into 32 s task blocks (either perception or imagery) separated by 32 s rest blocks, where subjects will view a fixation cross and await the start of the next block. The study will involve one imaging session that will last up to 2 hours.

Outcome Measures:

Our primary measure will be BOLD signal collected while participants view and imagine stimuli. Additional measures will be response time.

Analysis Procedures:

Our goal is to examine laminar BOLD signal responses during mental imagery and visual perception. To do this, we will use the T1- and PD-weighted images to construct a cortical surface model. The cortical surface model will be divided to yield estimates of the positions of different lamina. We will then apply these models to the fMRI data to generate estimates of the BOLD signal at each lamina. Single-subject data analysis (first-level) will comprise modeling

changes in the BOLD signal associated with each type of block (perception vs. imagery for each of the four categories). Data from the single-subject analyses will be carried forward into group analyses designed to test for task-dependent changes in laminar BOLD signals with a Task (perception vs. imagery) x Category (faces, places, tools, animals) x Lamina (infragranular, granular, supra-granular) ANOVA.

vii. *Topographical Organization of Category-Specific Cortical Areas in the Human Temporal Lobes (Martin)*

Experimental Procedures:

During an initial fMRI session (< 2 hours), we will use a multi-category functional localizer to identify cortical regions showing category-preferential activation in each participant individually. A single resting-state functional run (participants lie in the scanner and passively fixate on a centrally presented cross) will be acquired. Finally, 10 functional localizer runs will be acquired. Localizer runs will consist of a standard on/off block design, with 14 different category-blocks (20 s) per run, interleaved with short fixation blocks (10 s). During each category block, participants will view 20 images (500 ms) from a single category, presented at a rate of 1 image/s, with either 1 or 2 images repeating in immediate succession within any given block. Participants will be required to indicate via a button-press when they detect successive image repetitions.

Each participant will then be scanned in a second fMRI session (< 2 hours) 7 days following the first session. This second session will consist of 12 task runs with a standard rapid event-related design, during which participants will view images (pictures and words; 500 ms) from different categories in a pseudo-randomly intermixed order. For each image, participants will indicate via a button-press whether the content is “man-made” (e.g., tools, non-manipulable objects), “natural” (e.g., faces, animals), or “arbitrary” (e.g., scrambled images, pseudo-words).

Outcome Measures:

For localizer and task runs, our primary outcome measure will be the fMRI BOLD signal response measured while participants view images (pictures and words) from different perceptual and conceptual categories. For resting-state functional connectivity (rs-fcMRI) analyses, our primary outcome measure will be spontaneous low-frequency (< .1 Hz) fluctuations of the fMRI BOLD signal measured during resting-state runs.

Analysis Procedures:

Functional localizer analyses: We will use standard univariate general linear model analyses, contrasting the fMRI BOLD response to different categories of stimuli, to identify regions of interest (ROIs) representing category-specific areas across the cortex in each participant individually.

rs-fcMRI analyses: These category-specific ROIs will then be used as seed regions in rs-fcMRI analyses. The time-course of the spontaneous low-frequency BOLD signal fluctuations across the resting-state run within each ROI will be correlated with the time-course of every other voxel in the brain, producing whole-brain intrinsic functional connectivity maps. We will also examine the correlation of the time-courses between a priori defined pairs of ROIs to test specific hypotheses about the specificity of functional connectivity between these independently defined regions. Finally, we will use the recently developed “fc-Mapping” technique to determine whether or not the category-regions we identify using the functional localizer constitute functional “cortical areas”, as defined by consistent intrinsic connectivity patterns within the area, bounded by borders showing a sharp change in the distributed pattern of connectivity.

Task-related analyses: Several different analytic approaches will be used to assess task-evoked coupling of distributed networks of brain regions, as well as the nature of information represented within these category-regions.

We will use a data-driven multivariate approach (event-related PLS) to ascertain whether or not distributed task-related whole-brain covariance patterns reflect differences across these categories, as predicted, without using a priori GLM contrasts.

The localizer-defined ROIs will be used as seed regions in a multivariate task-related functional connectivity analysis (seed-PLS). Seed-PLS analyzes whole brain patterns of covariance associated with activity in a chosen seed ROI, driven by perceptual and conceptual processing of different categories of stimuli, thus revealing the dynamically changing patterns of functional connectivity that underlie these processes. We will ascertain whether or not there is task-related coupling of activity between category-specific regions and the relevant putative property-based/modality-specific regions during conceptual processing.

We will use univariate repetition priming analyses to assess category-specificity of repetition suppression of the fMRI BOLD signal across different categories of stimuli in whole-brain analyses and in ROI-based analyses using localizer defined ROIs. We will also combine seed PLS and repetition priming to assess our hypothesis that a local repetition-related reduction in BOLD signal within category-specific ROIs is associated with increased task-related functional connectivity of these regions with a broader domain-specific network.

Finally, we will use multi-voxel pattern analysis (MVPA) and multi-dimensional scaling (MDS) to answer a number of questions about category specific activations in ventral temporal cortex.

viii. *Elucidating the functional organization and topography of visual processing (Baker/Ungerleider)*

Experimental Procedures:

During individual scanning sessions, participants will view a variety of visual stimuli including pictures and videos of objects and scenes from a range of different categories (e.g. faces, body parts, beaches, kitchens, forests). Each image or video will be presented for a brief period of time (< 2 seconds for pictures and about 10 -15 s for videos) in blocked and event-related experiments and participants will be asked to make simple judgments about the stimuli. In some cases, participants will be given prior experience with some of the visual stimuli during separate behavioral training sessions. In each scan session we will obtain a number of MRI or MEG measurements, which may include structural scans, fMRI scans, resting state scans and DTI scans.

Outcome Measures:

Our primary outcome measures will be the MRI and MEG signals collected during the scans. The secondary outcome measures will be the behavioral performance during pre-exposure/training and during the scan sessions.

Analysis Procedures:

MRI and MEG data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

ix. *The role of top-down processing in visual cognition (Baker/Ungerleider)*

Experimental Procedures:

During both brain imaging and behavioral experiments, participants will be asked to perform working memory (e.g. delayed-match-to-sample) or imagery (e.g. visualization of individual named object images) tasks. Participants will be presented with visual (e.g. image of a cup) or

auditory (e.g. the word “cup”) stimuli and asked to remember, visualize the specific item, or engage in spontaneous thought.

Outcome Measures:

Our primary outcome measures will be the MRI or MEG signals collected during the scans. The secondary outcome measures will be the behavioral performance during pre-exposure/training and during the scan sessions.

Analysis Procedures:

MRI and MEG data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

x. *Body Representations in Cortex (Baker)*

Experimental Procedures:

In the MRI scanner participants will be presented with static and moving images of body parts (e.g. hand, leg, foot) either in isolation or interacting with another object (e.g. hand being brushed or touched, hand picking up an object). Participants may also be asked to perform particular motor actions such as clenching their fist or moving their fingers. Finally, somatosensory responsiveness may be tested using a MRI-safe tactile stimulator, which gives punctate tactile stimulation to different body parts with a calibrated von Frey filament at different frequencies (up to 5Hz).

Outcome Measures:

Our primary outcome measures will be the MRI signals measured during the scans.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

xi. *Task-dependent representations in cortex (Baker)*

Experimental Procedures:

During individual scanning sessions, participants will view a variety of visual stimuli such as objects from a range of different categories (e.g. animals, plants, furniture, vehicles, household items). On each trial the participants will be required to categorize the object images based on either the perceptual appearance of the object (stimulus-based perceptual judgments), or based on a conceptual knowledge of that object (conceptually-based judgments). Overall, there will be up to six tasks, half stimulus-based (color of the stimulus’ contour, detection of change in fixation cross, stimulus orientation) and half conceptually-based (real world size, movement and animacy). All the images will be presented under all the different task conditions, circumventing any associations between task and visual information. In each scan session we will obtain a number of MRI measurements, which may include structural scans, fMRI scans, resting state scans and DTI scans. Each participant will also complete an off-line behavioral experiment to independently assess his or her performance on the different tasks.

Outcome Measures:

Our primary outcome measures will be the MRI signals collected during the scans. The secondary outcome measures will be the behavioral performance inside and outside of the MRI scanner.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

xii. Deconstructing visual scenes in cortex (Baker)

Experimental Procedures:

During individual scanning sessions, participants will view images of artificial scenes created using Interior Design software to generate highly controlled “minimal” scenes, which allows to systematically manipulate object and spatial layout information in scenes. The minimal scenes are comprised of objects (e.g., chair, dresser, desk, etc.) placed on rudimentary background that can either be spatial (to varying degrees) or non-spatial (e.g. luminance gradient). A separate experiment will track the eye movements participants make, during the encoding and recognition of the minimal scenes. In each scan session we will obtain a number of MRI measurements, which may include structural scans, fMRI scans, resting state scans and DTI scans.

Outcome Measures:

Our primary outcome measures will be the MRI signals collected during the scans. Additional outcome measures will be the behavioral performance inside and outside of the MRI scanner and eye tracking patterns.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

xiii. Using eye-movements to investigate the representations of faces, objects, and scenes (Baker)

Experimental Procedures:

Participants may sit down in front of a computer screen or a real-world environment. If the head-mounted eye-tracker is used, a cap will be fastened to the participant’s head. Small infrared cameras attached to the cap will be positioned in front of their eyes. If the column eye-tracker is used, participants will rest their head into a column with a chin rest. Before and at certain points during the experiment, participants will perform a calibration of the eye-tracker, which involves looking at dots on the computer screen or at specific points in the real-world environment. Between calibrations, participants will be asked to do some task. Usually the task will involve looking at visual stimuli on a computer screen or in the environment and performing recognition, discrimination, or categorization on them or navigation through them.

Outcome Measures:

Measures will include the locations and durations of fixations and saccades of the eyes, as well as other behavioral measures such as reaction time, d-prime, and accuracy.

Analysis Procedures:

Data will be analyzed using standard software for looking at eye movements in addition to custom MATLAB scripts. We can contrast eye-movement patterns and other behavioral measures between stimuli (e.g. happy versus angry faces), as well as between tasks (e.g. categorization versus recognition), or participant groups (e.g. trained versus untrained).

xiv. Representation of visual word forms in cortex (Baker)

Experimental Procedures:

During individual scan sessions, participants will be presented with a variety of different words, pseudowords (e.g. ‘moop’) and consonant letter strings (e.g. ‘pmst’) in different fonts and sizes. Participants will be asked to make judgments on the stimuli (e.g. detecting repetition) or on the fixation cross. The primary focus of interest will be on responses in the visual word form area.

Outcome Measures:

Our primary outcome measures will be the MRI signals collected during the scans. Additional outcome measures will be the behavioral performance inside and outside of the MRI scanner.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

xv. *Neural circuits underlying word and sentence reading (Martin)*

Experimental Procedures:

During both fMRI and MEG experiments, participants will read words and will press a button when instructed (to ensure they are maintaining attention). Following the design of Pallier et al. (2011), words will be presented in trials consisting of scrambled words, 2-word phrases, 3-word phrases, 4-word phrases, or 6-word sentences. The content of these phrases and sentences will be one of four types: social-emotional, social, object, and pseudoword (which are not real words but look similar to real words). Social-emotional content will include words conveying feelings of happiness, sadness, anger, fear, surprise, disgust, and love taken from a database of norms on word valence and arousal (Warriner et al., 2013). Social content will only indicate people performing some task without any emotional content. Object content will refer to concrete objects. Phrases and sentences will be similar to those typically read in newspapers or young adult literature. For example, “Fran felt ill during the turbulence,” “The journalist was writing new columns,” “Tall lamp posts lit the avenue.” An example of a pseudoword sentence is “All zearts plored its denual dinvature.”

Outcome Measures:

Outcome measures will be accuracy on the trials instructing a button press and percent signal change for a given contrast between conditions in the fMRI and MEG experiments.

Analysis Procedures:

Differences in BOLD fMRI activity and MEG activity will be analyzed using repeated measures random effects models. The statistical maps will be thresholded at $q(\text{FDR}) < 0.05$, using the false discovery rate (FDR) approach for multiple comparisons correction. MRI, MEG, and behavioral data may also be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

xvi. *Human Auditory Mapping with High Magnetic Field Strength fMRI (Bandettini)*

Experimental Procedures:

To measure human audition gradients we will collect a series of functional scans while subjects listen to different patterns of structured sound. For the tonotopic mapping, subjects will listen to narrowband noise. For periodotopic mapping, the auditory stimuli will consist of broadband noise. A traveling wave methodology, equivalent to the one commonly used for primary visual mapping of eccentricity and polar angle, will be used. In brief, each stimulus of a given type, narrowband or broadband, will be presented in a block at a single value of center frequency or modulation rate, respectively. For example, for tonotopic mapping, stimuli will consist of 100-Hz-wide bands of AM noise centered at 400; 800; 1,600; 3,200; and 6,400 Hz, and amplitude modulated at 8 Hz. Stimuli used for periodotopic mapping will be broadband noise (e.g. 0–8,000 Hz) modulated at frequencies such as 2, 4, 8, 16, 32, 64, 128, and 256 Hz. The entire range of stimuli will be covered by consecutive blocks presented in order in what is referred to as a stimulus cycle, which will be repeated multiple time across scans to increase the available signal-to-noise ratio.

Outcome Measures:

The main outcome measure will be auditory field maps (AFMs) for bilateral primary and belt auditory areas for each participant of this study. For each region of interest, we will generate

maps of periodotopy and tonotopy. In the tonotopic maps colors indicate the preferred frequency range for each voxel (central frequency in Hz). In the periodotopy maps colors indicate the preferred period range for each voxels (Amplitude Modulation Rate in Hz).

Analysis Procedures:

After pre-processing and alignment of functional scans to the anatomical reference, we will conduct a voxel-wise Fourier coherence analysis to separate activity due to the stimuli (at the frequency of the stimulus cycles in each scan) from activity due to random and physiological noise (at the other frequencies in the cycles per scan domain). The phase assigned to each voxel with activity above a coherence threshold corresponds to that voxel's preferred point in the relevant stimulus space (e.g., a given voxel's phase may indicate that it is preferentially tuned to the 1,600-Hz-centered narrowband noise stimulus over the other narrowband stimuli). AFMs will then be defined individually for each hemisphere of each subject on a flattened representation of his/her cortex centered on Heschl's Gyrus.

xvii. *Is curvature processing functionally related to face processing? (Ungerleider)*

Experimental Procedures:

Behavioral task: Stimuli will include faces and scenes. During each trial, a stimulus image (a face or scene) will be presented briefly. Before and after the image presentation, a mask will be displayed briefly to interrupt visual processing. Subjects will be required to press a button if the stimulus image can be categorized as male/female, or forest/non-forest. Two kinds of masks will be used - curved and straight - yielding a 2 X 2 design (faces vs. scenes and curved vs. straight masks). The curved masks will be generated by filtering original images using curved Gabor filters, and the straight masks will be generated by filtering the original images using straight Gabor filters.

fMRI task: First, the following regions-of-interest will be localized for face processing: occipital face area (OFA) (Gauthier et al., 2000), fusiform face area (FFA) (Kanwisher, McDermott, & Chun, 1997), and anterior temporal face area (ATFA) (Rajimehr et al, 2008); for objects: lateral occipital complex (LOC) (Malach et al., 1995).

In order to uncover the curvature processing areas and their relationship to face processing areas, curvature processing areas will be localized by using the following four stimulus conditions: natural round shapes, natural rectilinear shapes, computer-generated sphere arrays, and computer-generated pyramid arrays. During the entire experiment, participants will be instructed to detect a color change of the center fixation dot while maintaining their fixation on the dot. In the same experiment, we will include checkerboard wedges to define retinotopic areas.

Outcome Measures:

We will measure subjects' behavioral performance (presentation times, error rate, and reaction time), and fMRI BOLD percent signal change during the scanning.

Behavioral outcome: We anticipate that participants will have lower accuracy in the curved mask condition than in the straight mask condition for faces, but higher accuracy in the curved mask condition than in the straight mask condition for scenes.

fMRI outcome: We anticipate the fMRI results will find the curvature processing areas in the human visual cortex as it was observed in macaque visual cortex.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical method, such as two-way ANOVA. fMRI data will be analyzed using a variety of standard technique including univariate and multivariate approaches.

xviii. Neurocircuitry involved in the representation of food (Martin)

Experimental Procedures: These experiments will include multiple types of food-related stimulus presentation, performed during behavioral or neuroimaging (MEG, EEG, or MRI) sessions. Two types of tasks may be used as follows.

Taste perception task: Some behavioral, MEG, EEG, or MRI sessions may be combined with gustatory stimulus delivery, in order to localize gustotopic regions in the brain. During these sessions, subjects may receive a sweet, bitter, salty, sour, or savory tastant, or a neutral solution, during testing. The neutral solution closely matches the properties of human saliva, and thus serves as a tasteless control stimulus. Tastants will be delivered to the subjects' mouths by our specially built computer-controlled, MR-compatible, pneumatic-pressurized tastant-delivery system (see Gustatory Stimulus Delivery in Study Procedures). During testing, subjects may undergo tastant delivery while either passively tasting and swallowing or while performing an orthogonal behavioral task, such as an oddball detection task. Either prior to or during testing, subjects may be asked to rate the tastants based on perceptual features such as identity, pleasantness, and intensity. These ratings will be used for subsequent statistical analyses or used as covariates for neuroimaging analyses.

Food picture task(s): Subjects may be asked to complete self-ratings of food preferences and eating behaviors, and they will be presented with photographs or videos of various types of foods, both during behavioral testing and during fMRI scanning. These depicted foods may vary in their specific taste attributes (sweetness, saltiness, etc.), in their caloric content, and in their overall pleasantness. Subjects may be asked to provide ratings of the pleasantness, identity, and taste attributes of those depicted foods. In addition to food pictures, subjects may also be shown non-food object photographs that will serve as a control condition. During fMRI scanning, food and object pictures may be presented while completing either an orthogonal behavioral task, such as a one-back picture repetition detection task (see Simmons et al. 2013), or a task requiring deliberate evaluative judgments of those picture stimuli (see Simmons et al. 2014). By comparing the activity associated with viewing food- and non-food stimuli, we will localize in each subject the brain regions supporting food perception in general. In addition, by varying picture presentation across multiple stimulus dimensions, we will localize brain regions preferentially responsive to those stimulus features.

Outcome Measures:

Primary outcome measures will include subjects' behavioral performance during testing (stimulus ratings, error rate, and reaction time), EEG or MEG signal, and fMRI BOLD percent signal change during task conditions.

Analysis Procedures:

MRI and MEG data will be analyzed using a variety of standard techniques including mass univariate analyses (general linear models of voxel time series) and multivariate approaches such as Support Vector Machine and Representational Similarity Analyses.

xix. How does the brain differentially represent visual information that informs action planning? (Ungerleider)

Experimental Procedures:

The project consists of two phases:

Phase 1) Behavioral:

Participants will rate the visual similarity of photographs or real objects either in person in a behavioral experiment on a computer or online. The photographs of the objects will be photographs taken of the real objects to be used in the neuroimaging experiment.

Participants will also be asked to grasp or reach for MR-safe objects (as determined by the MR Safety Committee) that will either be purchased or 3D printed for use in the experiment. Participants may be asked to perform the task in the mock scanner or seated at a table. If completed in the mock scanner, participants may be lying or seated on the bed with objects presented on the MR-safe table that was engineered for our use and has been approved by the MR safety committee (Figure 1). Using the table while lying on their back, participants will be able to see the table through the mirror as shown.

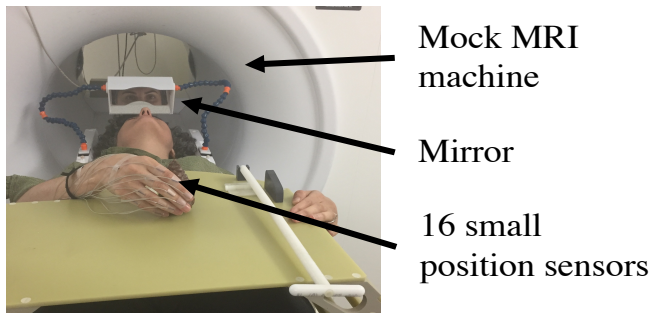


Figure 1. The MR-safe table set up used for object presentation and grasping in the mock scanner with the sensors shown or with the MR-safe glove in the actual MRI machine.

Body movements will be recorded using a body tracking device either Polhemus Liberty (<http://polhemus.com/motion-tracking/all-trackers/liberty>) which uses magnetic position sensors or a 5DT glove (<http://www.5dt.com/data-gloves/>) that uses fiber optic pressure sensors. The subjects may be video recorded while performing the actions. The face of the participants may be visible in videos. Appropriate video release forms will be obtained from the participants, and the videos will only be used according to the video release form (see Appendix 25H) The motion tracking data will only include the position of the body parts and will not include identifying information.

The data collected from the similarity ratings or motion tracking will be used to construct two object similarity matrices: 1) The visual similarity matrix; and 2) the grasp similarity matrix. These matrices will later be correlated with the pattern similarities obtained from fMRI data.

Phase 2) Functional MRI experiments:

Participants will be presented with the objects from Phase 2 in the real MR scanner. Participants may be asked to passively view, imagine grasping, reach without grasping, grasp the objects, or view videos of others grasping objects (collected in Phase 1 above). In the scanner, participants will wear an 5DT MR-compatible glove that records how the hand is being moved using optic fibers. Participants will wear single-use, medical-grade disposable gloves (either cotton or nitrile) under the recording glove to maintain proper hygiene. The subjects may be videotaped while in the scanner. Permission for videotaping will be obtained as described in Phase 1. Prior to the MR scan, subjects may complete a behavioral version of the task.

BOLD responses will be recorded and analyzed to determine the involvement of various brain regions in visual processing or action execution. This functional MRI experiment may take place in a single session or over multiple sessions depending on the pilot results. We will then use fMRI univariate and multivariate analysis techniques to measure the information content of each region for the shown objects. In the cases that grasping/reaching movements will be performed inside the scanner, arm movement and visual presentation may be separated in time to allow for separation of the visual and motor responses. The patterns of responses obtained in the fMRI experiment for each region will then be used to construct similarity matrices between objects. These fMRI similarity matrices will then be correlated with the visual and grasp similarity matrices. If a brain region only contains information about grasp-related features of the object, we expect to see higher

correlations between that region's fMRI similarity matrices and the grasp similarity matrix than that with the visual similarity matrix.

Each experimental session will not last more than 2 hours. Other than the main experimental runs, we may also include an anatomical scan as well as functional localizer scans to identify regions of interest for each subject for subsequent analysis. The localizer scans may take place in other experimental sessions due to time constraints.

In some experiments, instead of real objects, participants may be shown photos of objects on a screen in the scanner and asked to perform different tasks such as grasp to lift or grasp to use. Participants may also be asked to watch the experimenter perform the actions either in video or in person, or subjects may be asked to perform the actions in virtual or augmented reality rather than with real objects. We may perform eye tracking inside and outside the scanner in addition to body movement tracking. Similar experiments may be conducted using MEG and/or EEG.

Outcome Measures:

Outcome measures for this study will be ratings of visual and action similarity, reaction times, body movement measures, and brain activity.

Analysis Procedures:

The computer responses, eye movement, and body movement measures will be analyzed using common statistical techniques. Functional MRI, MEG, and EEG data will be analyzed using both univariate and multivariate techniques to determine differences in the average signal as well as differences in patterns of activity in each brain region across experimental conditions. We may also measure correlations between activities of different brain regions to assess their functional connectivity.

E. Plasticity and Priming (10 experiments)

i. What are the structural and functional correlates of learning visual associations? (Baker)

Experimental Procedures:

We will use diffusion tensor imaging (DTI), fMRI and behavioral experiments to investigate the role of the uncinate fasciculus (UF). First, we will measure the structural properties of the UF using DTI. Next, we will use fMRI to identify the distinct brain regions engaged during the processing of scenes (e.g. PPA) and faces (e.g. FFA) and characterize the structure of representations of a set of scenes (at baseline) within the regions of interest using an independent event-related fMRI experiment. We will then train the volunteers to learn associations between specific sets of indoor and outdoor visual scenes and individuals (six faces, oriented in three possible viewpoints). Once subjects show robust learning of the face-scene associations, we will repeat the fMRI experiment described above to measure the magnitude of change in the structure of representations of scenes that the subjects now associate with faces. Finally, we will perform correlation analyses between measures such as the learning rate in the behavioral task, changes in functional activity and or structure of representations with the tract measures, and explicate the relation between structural connectivity and the neural representations of visual associations.

Outcome Measures:

Our primary outcome measures will be the functional and structural MRI signals collected during the scans. The secondary outcome measures will be the behavioral performance during pre-exposure/training and measures of the architectural properties of white matter tracts, such as fractional anisotropy and mean diffusivity.

Analysis Procedures:

Functional and structural MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches. The relation between the behavioral profile and brain structure will be tested using correlation analysis.

ii. *Measuring training-dependent structural plasticity in adults with advanced MRI techniques (Baker)*

Experimental Procedures:

We will use motor and visual learning protocols in combination with advanced MRI techniques such as T1/T2 relaxometry that are very similar to standard structural scans but allow quantitative measures of the properties of white matter (e.g. myelin water fraction) to directly quantify the exact nature of the structural changes (e.g. myelination) following training. Healthy volunteers will be assigned to two separate training groups: motor and visual. Briefly, the motor task will involve learning to execute a sequence of complex finger movements rapidly with a particular hand, while the visual task will involve learning to detect a target from amongst distracters within a specific quadrant of the visual field. In both cases, subjects will be provided 1 hour of training in the assigned task, every day, for a period of up to two weeks. The learning profile observed in both tasks has been reported to comprise a fast phase marked by rapid learning within a day, and a slow phase that continues over weeks. Therefore, subjects will be scanned at up to five time points: baseline (T1), two weeks without training (T2), immediately after the first training session (T3), one day after the first training session (T4) and two weeks after training (T5). The scans between T1 and T2 will serve as within-subject control scans and the scans at T2, T3 and T4 will be used to measure structural changes mediating the fast and slow phases of learning. Taken together, this experiment design will potentially provide the strongest evidence for training-specific structural changes as the effects of training will be (a) specific to the training task (Motor/Vision), (b) specific to particular brain regions (Trained hemisphere), and (c) correlated with behavioral measures of training.

Outcome Measures:

Our primary outcome measures will be the MRI signals collected during the scans. The secondary outcome measures will be the behavioral performance during pre-exposure/training and quantitative measures of longitudinal changes in brain tissue such as T1 and T2 relaxometry as well as measures of changes in white and gray matter architecture.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches. The relationship between the behavioral profile and brain structure will be tested using correlation analysis.

iii. *Somatosensory perceptual learning (Baker)*

Experimental Procedures:

Here, we will use the “Helix”, a multi-modal, MR safe tactile stimulator that allows precise and reproducible presentation of tactile stimuli to a given finger in a fully interleaved, random fashion both in and outside the MRI scanner. Briefly, healthy volunteers will be tested and trained for five consecutive days on a tactile discrimination task. One group of participants will be trained with either the index or ring finger of the dominant hand, while another group will be trained with the same finger of the non-dominant hand. The two groups of participants will then be tested with the trained finger and the untrained fingers in both the trained and untrained hands. The tactile stimuli comprise small rectangular patches of embossed stimuli on a rotating drum. For example, stimuli varying in roughness can be created with embossed dots. Changes in

the size and spacing between dots vary the sensation of roughness. Equivalent stimuli can be presented in the visual domain. Participants will be trained on tactile stimuli only, visual stimuli only, or on both visual and tactile stimuli. Structural and functional MRI scans will be acquired at baseline, before the start of training, and after training.

Outcome Measures:

Our primary outcome measures will be: i) accuracy and reaction time during the behavioral training; ii) the MRI signals collected during the scans.

Analysis Procedures:

MRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches. The relation between the behavioral profile and brain structure will be tested using correlation analysis.

iv. *Effect of object repetition on neural tuning curves (Martin)*

Experimental Procedures:

Each participant will engage in three sessions for the experiment: 1) a behavioral session in which pictures of common objects (either animals or tools) are identified repeatedly using behavioral tasks such as naming, 2) an fMRI session in which animal pictures are presented in short adaptation sequences, with intermixed baseline periods and pictures of man-made objects to which subjects are instructed to press a button, and 3) a subsequent behavioral session in which the animals that were novel or repeated adaptation "anchors" during fMRI are presented for naming. In sessions 1 and 3, participants are shown the pictures on a laptop computer in a quiet testing room in the NMR center with naming responses and latency recorded by a microphone. In a single trial, a visual fixation cross is presented for 500 ms, followed by the picture to be named for 200 ms, followed by an intertrial interval of 1800-2300 ms during which a naming response is given. During session 2 (fMRI), the participant will remain in the MR scanner for a period up to two hours. Structural and functional MRI scans will be performed. Cardiac (finger ECG) and respiratory signals (respiration belt around the abdomen) will be recorded for later off-line removal of physiological artifacts in the BOLD response. Participants will be asked to maintain fixation on a cross presented at the center of a screen mounted directly behind the head, visible via a coil-mounted mirror. Pictures will be presented at a rate of 1 per second, with a picture duration of 200 ms that is replaced with the fixation cross for 800 msec. Pictures will consist of: 1) adaptation sequences of animal pictures (3-7 sequential presentations of an anchor picture, either previously named in session 1 or novel, followed immediately by a single related or unrelated deviant picture), 2) man-made object pictures (e.g. tool) to which participants are required to provide a button press response, or 3) baseline pictures that are phase-scrambled versions of the animal pictures (i.e. with the same low-level image characteristics). The deviant animal pictures that finish each adaptation sequence can be related either as "exemplars" of the same type of animal (e.g. a different depiction of the anchor animal from a different point of view) or as conceptual associates (e.g. for a "dog" anchor, a picture of a "cat") or unrelated (e.g. for a "dog" anchor", a picture of a "lobster").

Outcome Measures:

Outcome measures in sessions 1 and 3 will be naming accuracy (scored by the experimenter) and response time in ms (marked by voice onset with the microphone relative to picture onset). For session 2, the outcome measures will be the fMRI signal collected while participants view adaptation sequences (with either previously named or novel anchors, crossed with anchor-deviant relationships of exemplar, conceptual associate, and unrelated), as well as accuracy in

detecting man-made object pictures (~ 30 per scanning run; mainly to insure that participants attend to all of the pictures).

Analysis Procedures:

Our goal will be to examine the relationship between object repetition (novel vs. previously named anchors) and the mean BOLD response in each brain voxel to both anchor and deviant stimuli, with tuning curves measured primarily to the deviant stimuli. Behavioral measures taken before and after fMRI (in sessions 1 and 3) can then be related to any changes with repetition observed during fMRI (session 2). FMRI analyses will be done in both a whole-brain approach and using regions of interest (ROIs) calculated from condition contrasts (e.g. First vs. Last Anchor, Last Anchor vs. All Deviants, Novel versus Previously Named Anchors). fMRI data processing will use the standard AFNI pipeline, including ANATICOR to remove physiological and hardware artifacts, 3dANOVA to evaluate the effects of condition contrasts, and 3dttest++ to examine fMRI-behavior correlations.

v. *Effect of object repetition on neural response magnitude, regional interactions, and identification performance (Martin)*

Experimental Procedures:

Each participant will engage in three sessions for the experiment: 1) a behavioral session in which pictures of common objects (animals, tools, etc.) are identified repeatedly using behavioral tasks such as naming, 2) an fMRI session in which pictured objects, either previously named or novel, are presented for identification using one of two possible tasks (object naming versus an unrelated discrimination on the fixation cross presented in front of the object), and 3) a subsequent behavioral session in which the objects that were novel or repeated during fMRI are presented for naming. In sessions 1 and 3, participants are shown the pictures on a laptop computer in a quiet testing room in the NMR center with naming responses and latency recorded by a microphone. In a single trial, a visual fixation cross is presented for 500 ms, followed by the picture to be named for 200 ms, followed by an intertrial interval of 1800-2300 ms during which a naming response is given. During session 2 (fMRI), the participant will remain in the bore for a period up to two hours. During which time structural and functional MRI scans will be performed. Cardiac (finger ECG) and respiratory signals (respiration belt around the abdomen) will be recorded for later off-line removal of physiological artifacts in the BOLD response. Participants will be asked to maintain fixation on a cross presented at the center of a screen mounted directly behind the head, visible via a coil-mounted mirror. Each picture will be presented for a duration of 300 ms, followed by a delay of 7-14 seconds in multiples of the TR. For the naming task, participants will be asked to name the object as quickly and accurately as possible (either naming silently to themselves while pressing a button, or naming overtly with the response recorded using an MR-compatible optical microphone with active noise cancellation (Phon-Or, Inc.). For the unrelated discrimination task, participants will be asked to judge if the fixation cross, superimposed on top of the picture, has grown "wider" or "taller" during picture presentation, providing their response with a button press.

Outcome Measures:

Outcome measures in sessions 1 and 3 will be naming accuracy (scored by the experimenter) and response time in ms (marked by voice onset with the microphone relative to picture onset). For session 2, the outcome measures will be the fMRI signal collected while participants view either novel or repeated (previously named in session 1) pictures, as well as naming accuracy/latency (naming task) or accuracy/latency in the "wider"/"taller" judgments (unrelated discrimination task). As this is a slow event-related fMRI design, we will be able to extract the fMRI response

on each trial for use in calculating correlations across trials between pairs of brain voxels/regions.

Analysis Procedures:

Our goal will be to examine the relationship between object repetition (novel vs. repeated conditions) and the mean BOLD response in each brain voxel, object repetition and the correlation of the single-trial responses across pairs of brain voxels/regions, object repetition and identification speed/accuracy, and the relationships among these three separate phenomena. This will be done in both a whole-brain approach and using regions of interest (ROIs) calculated *from* condition contrasts (e.g. Novel versus Repeated Stimuli, Novel+Repeated versus baseline). fMRI data processing will use the standard AFNI data pipeline, including ANATICOR to remove physiological and hardware artifacts, the function 3dTcorrMap to evaluate whole-brain voxel-level correlations, and 3dttest++ to examine fMRI-behavior correlations.

vi. *The mechanism of emotional memory consolidation and reconsolidation (Baker)*

Experimental Procedures:

During both brain imaging and behavioral experiments, participants will be asked to perform an associative memory task, in which neutral cues are associated with emotional stimuli. A neutral cue will be one of three possible types: neutral sounds (human voice pronouncing pseudo-words), images (common objects, neutral faces, or scenes), and combination of those sounds and images. Half of the neutral cues will be associated with other neutral stimuli such as neutral scenes or sounds, and the other half will be associated with negative emotional stimuli. These emotional stimuli will be one of the following types: electrical stimulus (Lissek et al., 2010; Schiller et al., 2010; Visser et al., 2013), IAPS image (Lang et al., 1998; Sabatinelli et al., 2005), or aversive sound (such as human scream and 90-100 dB aversive tone (Lau et al., 2011)). The delivered intensity of electrical stimulus (shock) will be individually adapted to be unpleasant, but not painful within the range of 0.1 – 5 mA (to the hand, Lissek et al., 2008).

The associative memory task comprises one learning session and one or two retrieval sessions under short-term and long-term paradigms. In the short-term paradigm, the time intervals between the learning and retrieval sessions will be less than 3 hours, and in the long-term paradigm, the intervals will be more than 1 day. In the learning session, for about 60 min, participants will be repeatedly exposed to 6-40 neutral cues, 20–50% of which will be followed by an emotional stimulus. In the retrieval sessions, participants will be repeatedly exposed to each cue without emotional stimulus. For the first 10-30 participants, the learning and retrieval sessions will be conducted outside the scanner, and for the next 10-30 participants, the sessions will be performed inside the scanner. During all the learning and retrieval sessions, skin conductance (galvanic skin response) via sensor on the finger tips or surrounding regions, pupil dilation via eye tracker, heart rate (electrocardiogram) via electrodes placed on the left and right forearm and/or startle reflex (electromyography) via electrodes placed under the eye will be measured to assess automatic fear response. In addition, participants will be asked to press buttons when they see or hear the cues to express their explicit associative memory.

Emotional stimuli including electrical shock, negative emotional pictures, or aversive sounds may produce discomfort. The intensity of electrical shock, which is determined individually prior to conditioning, will be as low as possible. Participants will be exposed to examples of the IAPS images or the auditory tone prior to starting the experiments to assess whether participants are distressed or negatively affected by the pictures or sounds.

Participants will be free to stop the experiment at any time during testing.

Outcome Measures:

Correlation between fMRI data and behavioral data (e.g., eye tracking data, skin conductance data, reaction times and responses) will be the primary outcome measure.

Analysis Procedures:

fMRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches. The relationship between the behavioral profile and fMRI data will be tested using correlation analysis.

vii. *How does memorability of stimuli influence memory and perception? (Baker)*

Experimental Procedures:

Participants will perform perceptual tasks where they will be asked to view and/or categorize a stimulus, as well as memory tasks where they will be asked to study and remember certain stimuli. These stimuli will be selected to vary in their memorability. During these tasks, the participant may be asked to either focus or divert their attention from the main stimulus. To increase participants' motivation to perform accurately on the memory tests, they may be offered additional monetary rewards of up to \$20 for good performance. Monetary rewards may be offered based on performance on a task either on a trial-by-trial basis or at the end of the experiment. For example, in a memory task, participants may receive additional compensation on every trial (for e.g., 10 cents for every picture remembered correctly), or in a perceptual task, participants may be rewarded at the end of the experiment (for e.g., an additional \$10 if they label indoor and outdoor scenes with greater than 95% accuracy). These amounts will be in addition to the existing compensation for behavioral or MRI/MEG studies. As participants perform these tasks, we will record behavioral, fMRI, MEG, eye tracking, and/or physiological data. After tasks in the scanner, participants may be asked to complete additional behavioral tasks outside the scanner, for example to measure their memory performance for stimuli they saw in the scanner.

Outcome Measures:

Outcome measures for this study will be reaction times, behavioral performance and memory performance on the behavioral tasks, physiological measures (e.g., heart rate, galvanic skin response), eye tracking measures, and brain activity (fMRI, MEG).

Analysis Procedures:

The outcome measures will be combined and analyzed using classifiers and other multivariate techniques to uncover patterned differences in behavior, brain activity, eye movements, and physiological measures based on stimulus memorability, as well as individual memory performance. Univariate analyses will also be conducted to analyze the relationship between BOLD activity (in fMRI) and MEG signal and memorability and memory.

viii. *Using naturalistic and dynamic memory stimuli to investigate how the brain represents episodic memories over time (Baker)*

Experimental Procedures:

This experiment will analyze the memory traces and neural signatures for people viewing naturalistic memory video, auditory, or photographic stimuli from their own lives. People in the United States who have used the 1 Second Everyday app for at least two months collecting brief videos, sounds or photos of their life, and are willing to participate in an MRI scan while viewing their recorded videos will be recruited for this study.

The 1 Second Everyday app is a platform that lets users clip videos they have taken on their phone into one-second snippets and then compiles them into a long video consisting of a series of days; it is essentially a simple video-editing application (see screenshots in Appendix 25F).

The experiment in this protocol will not use the app, but will only use content created by the app. The video clips that are generated by the app are saved locally to the user's phone – they are never uploaded to any servers, and the app developers do not have access to the videos, nor do they claim rights to the user's videos (see Terms and Conditions and Privacy Policy, attached; they only claim rights if users intentionally upload their videos to crowd-sourced general public “community videos” within the app). Videos thus remain securely on the users' phones. Many users, however, share their videos with others on YouTube or other social media sites, as this app is as much a social media phenomenon as it is a way for tracking memories. A quick search of YouTube with the 1 Second Everyday twitter tag (#1SE) returns over 34,000 videos alone. Although the videos are compilations of brief, one second clips and contain limited identifiable information, users often subjectively report that the single second is able to help retrieve a rich memory for an entire day. An example video compilation can be seen here: <https://www.youtube.com/watch?v=bQxAYAo6sn4>.

Recruitment will be mainly conducted through the “1 Second Everyday App” using an IRB approved banner ad. However, any of the strategies described below (see Appendix 25C-2 for examples of recruitment material) and in the Recruitment section on page 50 may be used. Flyers may be posted on bulletin boards at the NIH Clinical Center or placed in libraries with approval of the venue or in accord with their policy. Flyers may be made available at speaking engagements related to the app with approval of the venue or in accord with their policy. Flyers may be given directly to those requesting study information. IRB-approved ads will be posted on listservs with the permission of the moderator and IRB-required statement on how the receiver was identified. Listservs may include those of the NIH community. Short text recruitment banners may be used in print and digital publications with venues such as the NIH Record or CC News.

In terms of recruitment through the app, the app periodically has a banner that shows news or tips related to the app when the app is opened (see Appendix 25F - Figure 2). When users click on the banner, they are directed to a separate web page. The app does not collect any information on who clicks on the banner – it is just a simple link (confirmed by discussions with the app developer, Cesar Kuriyama). The app also does not contain any other advertising or use third-party advertising services. A small banner will be used on the app, and when clicked on, users will be directed to a recruitment page hosted on the NIMH website. Note that 1 Second Everyday has a large user base, with over 1,000,000 downloads in the United States, so being a user of the app does not immediately identify participants of the study. Participants will be asked if they are aware of anyone they know also participating in the study, to avoid showing videos of a participant to someone they know.

Once users decide to participate in the study, they will be asked to provide us with a selection of their videos, sounds, and/or images. Users will send us the videos through secure NIH communications, and they will be stored on secured, password-protected NIH computers in locked offices. The experimenters will screen the stimuli to ensure they do not include highly emotional images (such as violent or sexual content) as well as clips that may show illegal or sensitive material. Additionally, the experimenters will limit stimuli used to those obtained in public, to the extent possible. At the time of the experiment, we will collect behavioral, fMRI and MEG data while participants view stimuli created by this app. Participants will view a mix of their own videos and videos from one other randomly selected participant. The videos from the other participant are to serve as control stimuli, so that two participants have exactly the same perceptual experience (i.e., they are seeing the same videos), but different memory experiences

(half of the videos are meaningful to one participant while the other half are meaningless, and the reverse for the other participant). Other methods of creating control stimuli would lack several of the features of naturally-generated videos, as it is impossible to artificially account for all the variables that would be present in videos taken over the course of several years (e.g., seasonal changes, camera quality changes, major world events). As social interaction with familiar people is also an essential component to one's memories, both face- and scene-based memory videos will be necessary. As each participant's videos will only be seen by one other randomly selected participant, it is unlikely that this participant or other people in the videos will be identifiable. Additionally, the videos from both participants are only a second long, will be viewed a single time each, and will be presented in a randomized, intermixed (between participants), non-chronological order, so that it will be nearly impossible to construct meaningful information from viewing another participant's videos in the experiment.

As participants view the set of stimuli, they may be asked to make judgements on these stimuli (e.g., judging their memory strength or emotional content). We may also collect physiological measurements such as galvanic skin response, heart rate, or temperature, and may also collect eye movement data while participants are viewing these videos. After the scan, participants may be asked to complete a behavioral memory task or asked to label the stimuli for information such as location, memory strength, or emotional ratings about their own videos.

Outcome Measures:

Outcome measures for this study will be mainly the neural activity (fMRI, MEG) for participants when viewing their memory stimuli as well as control stimuli. We will also collect measures of reaction times, behavioral performance, and physiological measures (e.g., heart rate, galvanic skin response) and eye-tracking measures.

Analysis Procedures:

Univariate and multivariate analysis techniques will be used to uncover differences in brain activity (fMRI and MEG) based on the time the memory was encoded. These differences will be compared with the control stimuli, that have similar rich perceptual information and were encoded at different times by another participant, but have no memory information for that participant. We will also analyze the degree to which spatial location of the memory, emotional ratings, subjective ratings of memory strength, and other behavioral or physiological measures taken relate to this brain activity as well as to visual and auditory features in the memory videos themselves. Preliminary analyses of pilot data show patterns of neural activity highly specific to individuals' own memories, in regions identified to be important to memory, such as the hippocampus. However, due to the large variation in visual content of participants' videos (e.g., some participants tend to record more scenes, others tend to record more faces, etc.), a larger number of participants would better allow us to have enough samples of different visual content types. Thus, expanding the pilot to a larger scale main experiment with 72 participants will ensure that our findings generalize across different types of visual memories.

ix. Which brain regions and circuitry mediate visual statistical learning? (Ungerleider)

Experimental Procedures:

Participants will be asked to view and classify stimuli as belonging to predefined categories (for example, classifying images as either animate or inanimate). The stimuli will be grouped into different blocks of either 'structured/patterned' or 'random' images. In the 'structured/patterned' blocks, unbeknownst to the subjects, the presentation of the images will follow a pattern (e.g., the images will be presented in a particular order 121122, where 1s represent animate and 2s

inanimate images). In the ‘random’ block, the images will be chosen in random from both the categories for classification.

Subjects will undergo fMRI, MEG, or EEG (with and without fMRI) while performing the categorization task and/or while passively viewing the ‘structured/patterned’ and ‘random’ blocks of images. We will record reaction times and accuracy while the subjects perform the task. Eye tracking data may also be recorded. We may also record physiological measures (e.g., heart rate, galvanic skin response) in the scanner to account for noise in the fMRI data due to physiological changes. After completion of the categorization task behaviorally and/or in the scanner, subjects may be asked to complete additional tasks, for example, complete a questionnaire about their experience and strategies undertaken while performing the task.

We hypothesize that the subjects will implicitly learn the embedded patterns in the ‘structured/patterned’ blocks while performing the categorization task. The analysis of differences in the behavioral and neural measures during the presentation of ‘structured/patterned’ and ‘random’ blocks of images will help us understand the neural mechanisms of visual statistical learning.

Outcome measures:

Outcome measures will be reaction times, accuracy, physiological measures (e.g., heart rate, galvanic skin response), eye tracking measures, and brain activity (fMRI, MEG or EEG signals).

Analysis Procedures:

The outcome measures will be analyzed using standard parametric and non-parametric statistical tests, like ANOVA, Wilcoxon-signed rank and Wilcoxon rank-sum test. To uncover patterned changes in behavior and neural activity we may use machine learning, univariate, and multivariate approaches.

x. *What are the neural correlates of novel skill learning? (Baker)*

Experimental Procedures:

This experiment will investigate the motor and neural correlates of prosthesis skill learning through training two-handed participants on a prosthesis hand simulator. Participants will need to learn new motor kinematics (alternative to basic hand kinematics) to operate the prosthesis. Healthy two-handed participants willing to participate in an MRI scan and undergo the prosthesis training regimen, will be recruited for this study. Participants will train on an MRI-compatible prosthetic hand simulator, a myoelectric prosthetic hand attached to one of their hands, controlled by EMG sensors. Training will include 7-14 (1-2 hour) sessions of training on unimanual and bimanual tasks, derived from activities of daily living with high practicality (e.g. opening a bottle of water, making a cup of tea). During training, we will record behavioral, eye tracking and physiological data. Before and after training, we will collect fMRI, MEG and EEG data. During neuroimaging sessions, participants will engage in (i) viewing visual stimuli, (ii) motor imagery tasks, and (iii) motor action tasks. For motor action tasks in the scanner, participants will move individual body parts and perform simple movements (open-close, reach to grasp, etc.) with their hands and the MRI-compatible prosthesis training device.

Outcome Measures:

Outcome measures for this study will include accuracy and reaction times on training tasks, questionnaires, assessments of motor performance (motor error, motor variability, changes in speed-accuracy response), eye tracking measures, physiological data, and brain activity (fMRI, MEG, EEG).

Analysis Procedures:

Behavioral, eye-tracking and physiological data will be analyzed using MATLAB, python and other analytical programs. Non-parametric and parametric statistical analyses will be performed using statistical software packages such as SPSS. Neuroimaging outcome measures will be analyzed using standard univariate and multivariate techniques.

F. Moral and Social Cognition (5 experiments)

i. The neural systems responding to care-based transgressions as a function of severity (Blair)

Experimental Procedure:

Participants will view images of care-based transgressions (e.g., one person threatening another) and prosocial actions (someone giving to charity) and asked to judge whether the action is appropriate or not. The transgressions and prosocial items will be graded by intensity on the basis of previous work and thus allow the identification of systems responding to these items that show modulation by intensity.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

ii. The neural systems mediating the distinction between care-based and conventional transgressions (Blair)

Experimental Procedure:

In this study participants will be presented with line drawings of actions (e.g., one child hitting another, one child talking to another in class) and asked to decide whether the action is OK to do in two school contexts: A “strict” school where all rules are strictly enforced and a “relaxed” school where no actions are prohibited.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

iii. The impact of audience on the neural response to care-based and conventional transgressions (Blair)

Experimental Procedures:

In this study, participants will be presented with brief vignettes of care-based and conventional transgressions that occur either in the presence or absence of an audience. Participants respond by button press when they have read the vignette.

Outcome Measures:

Outcome measures for this study will be reaction times, responses and percent signal change in the fMRI experiment.

Analysis Procedures:

Behavioral data will be analyzed using standard statistical tests such as ANOVA and t-tests to determine differences in reaction time and accuracy. fMRI data will be preprocessed and analyzed using standard procedures (Cox, 1996). Correlations between behavioral measures and brain activity will also be computed.

iv. The neural mechanisms of social provocation (Blair)

Experimental Procedures:

Participants will be presented with a variant of the Ultimatum game (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). Participants will be informed they are playing a game with a series of partners (which they will understand to be computer controlled). During the game participants encounter 12 partners who are indicated by name. Trials are presented randomly. At the outset of each trial, the partners have \$20 and the participant has \$3. During the offer-phase (3000ms), the partner offers to divide their \$20 with the participant either fairly (e.g. \$10 to participant; \$10 to partner) or unfairly (e.g. \$6, \$4, \$2 to participant; \$14, \$16, \$18 to partner). A 500-3500ms randomly jittered interval follows the offer-phase. During the decision-phase (4000ms), the participants use a button press to indicate whether they wish to i) accept the partners offer and give up their \$3 in exchange (e.g. receive \$10 from the fair offer) or ii) to spend some of their \$3 in order to punish to the partner. Participants have the option to spend \$1, \$2 or \$3 and cost the partner \$7, \$14 or \$21 respectively. Next, during the outcome-phase (3000ms), the results of the participants' choices are displayed (e.g. partner gets -\$1, you get \$0), followed finally by a second 500-3500 randomly jittered interval preceded the next trial. Each participant will be exposed 120 trials (60 fair trials, 24 \$14/\$6 trials, 24 \$16/\$4 trials and 12 \$18/\$2 trials) over four 6 minute 52 second runs. Participants will be free to stop the experiment at any time during testing.

Outcome Measures:

fMRI data (BOLD response) will be the primary outcome measure.

Analysis Procedures:

fMRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

v. The impact of animacy on threat processing (Blair)

Experimental Procedures:

The looming task involves the presentation of four different types of images: (i) threatening and animate (e.g. snarling dogs); (ii) threatening and inanimate (e.g. pointed gun); (iii) neutral and animate (e.g. sitting rabbit); or neutral and inanimate (e.g. a mug). All animate stimuli are animals and all inanimate stimuli are objects presented on their own (i.e., no hand was holding the gun/mug). The stimuli were taken from previous work (Yang, Bellgowan, & Martin, 2013).

Each trial involves the *rapid presentation of the same image 4 times* (250ms per presentation). Each presentation involves the image taking up a greater (or lesser) extent of the screen. Thus, for *looming trials*, centered images occupy 25%, then 50%, then 75% and then 100% of the screen. For *receding trials*, centered images occupy 100%, then 75%, then 50% and then 25% of the screen. Following these presentations is a 1250ms fixation. Participants simply respond via button press as soon as they perceived the image. The task involves 4 runs of 5 minutes and 59 seconds, each consisting of 80 image trials (20 of each of the 8 trial types) and 60 2000ms fixation trials. Participants will be free to stop the experiment at any time during testing.

Outcome Measures:

fMRI data (BOLD response) will be the primary outcome measure.

Analysis Procedures:

fMRI data will be analyzed using a variety of standard techniques including mass univariate and multivariate approaches.

G. Methods development and evaluation (9 experiments)

i. Comparing uni- and multivariate statistical analysis (Averbeck)

Experimental Procedures:

During each of three scanning sessions, participants will be asked to maintain fixation on a red cross presented at the center of a screen mounted directly behind the head, visible via a coil-mounted mirror. After three acclimation trials in which three scrambled pictures are presented, a series of 60 pictures (30 emotional and 30 neutral) that depict people in various situations will be presented in a slow event-related fMRI design. Each picture will be presented for two seconds, followed by a 10-12 s fixation only period. The pictures are selected from the International Affective Picture System (IAPS), an image database containing emotionally evocative, color photographs that represent a wide range of semantic categories. Four novel picture series will be presented during each session and within a session participants will view each series twice (i.e. participants view a total of 480 pictures). While viewing these images, participants will perform an ancillary change detection task, where they are asked to respond with a button press whenever the color of the fixation cross changes from red to blue. MR slice acquisition will be oriented in an oblique axial plane such that sampling of medial prefrontal cortex, amygdala, insula, ventral striatum, inferotemporal cortex, and middle occipital gyrus is obtained. The placement will be tailored for each participant and tilted for optimum coverage of areas of interest, and if possible, to exclude sinus cavity coverage, as a means of limiting susceptibility artifact.

Outcome Measures:

Our primary outcome measure will be the fMRI signal collected while participants view either neutral or emotional images. As we will use a slow event-related design, we can extract the fMRI response on each trial. We will also examine accuracy in detecting the dimming of the cross, but only to make sure participants were on task.

Analysis Procedures:

Our goal will be to examine the relationship between decoding approaches and mass-univariate approaches, and relate them analytically using Fisher Information. To do this we will extract an ROI with approximately 100 voxels from each participant's data. The noise covariance matrix (i.e. the covariance matrix of the residuals of the response across trials) for these voxels, as well as the average response of the voxels in each of the two conditions will be calculated. Plots of the eigenvalues of the noise covariance matrix, as well as the projection of the signal vector (defined as the vector of the difference in response between conditions) on the eigenvectors will also be generated. This will allow us to examine the relationship between the signal and the noise in the system. Fisher information can be converted to estimates of decoding performance, and this can be compared to actual decoding performance (see Averbeck and Lee, 2006).

ii. Multivariate analysis fMRI experiments (Bandettini)

Experimental Procedures:

During each scanning run, healthy participants will be asked to perform some tasks shown on the screen. The task may be passive viewing with some trials that have simple instructions to main

the attention of the participant. The task may also be to discriminate categories of object shown on the screen. The tasks are implemented by a Python based and free toolbox, called “PsychoPy”. While the participant are performing the tasks, T2* weighted EPI are acquiring spontaneously. T1-weighted structural volume will be acquired after completing the task runs. Standard TR and voxels size are used, based on filed of the scanner. However, in order to reduce inter-run variability, it is preferred to have a long run that contains more than one task than one run per task.

Outcome Measures:

The outcome measures will be the EPI images that carry the BOLD signal when the participant performing the tasks. Responses for the tasks are also collected on the remote computer outside the scanner room.

Analysis Procedures:

Voxels in the grey matter mask or selected ROI will be extracted. We can either average the voxels in each stimulus trial (in the temporal dimension) (Chu et al., 2011a), or we can apply standard mass-univariate method to obtain the parameter maps (beta maps) for each stimulus trial. Those temporally compressed voxels will be used as the input features $\{x\}$ for pattern classifiers (e.g. Support Vector Machine, Linear Discriminate Analysis, Logistic Regression). The corresponding labels $\{y\}$ for each sample of feature are defined by the condition of the corresponding stimulus. Part of the feature label pairs $\{(x,y)\}$ will be left out, and the remaining pairs are used to train the classifiers. After the training, those features left out in the process of training will be used to compute the predicted label from the trained classifier. The true labels are compared with the predicted label to calculate the classification accuracy. Classification accuracy and pattern reproducibility measure the amount of information encoded in the brain for the corresponding experimental conditions.

iii. Development and Evaluation of perfusion imaging sequences (Bandettini)

Experimental Procedures:

For PASL, PICORE QUIPSSII (Wong et al., 1998) will be employed with TI1/TI2/TR=600/1500/2000 ms, 10-cm tagging area, and 1-cm gap to the imaging slab. For PCASL, balanced design (Wong et al., 2005) will be used with 1600-ms labeling period, 900-ms post-labeling delay, and TR=3000 ms. EPI images will be acquired with 8 5-mm axial slices, 24-cm FOV, 64 x 64 matrix, 90° flip angle, 18-ms TE, and SENSE=2. The tagging location will be aligned to the PASL tagging slab to result in the same gap to the imaging slab placed in a way to avoid tagging in the transverse segments of the main feeding arteries. The design allows for different tradeoff between temporal resolution and SNR but maintaining the same transit delay for PASL and PCASL. Functional tasks will consist finger tapping (motor), flashing-checker board (visual), and n-back (memory) stimuli. Both motor and visual tasks will be performed with block designs of on/off at 5/10, 10/20, and 20/40 s, respectively. The n-back task will be performed with 20/40 s only. A total of 14 runs of 5-min long will be obtained with PASL and PCASL. The imaging slab will be positioned differently among motor, visual and memory tasks in a way to examine the effects of tagging location. In addition, to examine the inhomogeneity sensitivity of PCASL, two extra PCASL runs will be acquired with 10/20 and 20/40-s on/off frequency for visual tasks using a recently developed pre-scan procedure (Luh et al., 2010) to correct for off-resonance effects at the tagging location. The study will be carried out on both 3T and 7T.

Outcome Measures:

The primary outcome measure will be the baseline CBF and CBF changes during functional activation. The effects on task frequency can be examined with two different temporal resolutions. The SNR, contrast-to-noise ratio, temporal SNR, and activation amplitude and size of ASL signal can be derived as measures of performance in addition to the effects of inhomogeneity correction for PCASL.

Analysis Procedures:

CBF values will be derived from ASL signal using surround subtraction (7), coil sensitivity correction and the General Kinetic Model (Buxton et al., 1998). BOLD weighted signal can also be derived from surround addition even though the TE is not optimized with T2* weighting due to high SNR at 3T and 7T. Activation will be identified with GLM to both CBF and BOLD time courses. Each epoch of on/off period will be averaged together to examine the temporal dynamics of CBF and BOLD changes during task transition as a function of task frequency and temporal resolution. The baseline CBF will be used to derive relative tagging efficiency of PCASL to PASL and the changes from inhomogeneity correction. The comparison of CBF and BOLD will provide information on coupling of CBF and cerebral blood volume at different brain regions. The temporal SNR will be compared as a function of ASL technique, brain area and field strength in addition to the correspondence to estimation from theoretical model.

iv. *fMRI calibration and non-neural noise removal (Bandettini)*

Experimental Procedures:

fMRI data will be collected from volunteers using multiple conditions. “Resting” scans will be used for baseline measures of fMRI variation and to test how methods alter functional connectivity between regions. Task data from other parts of this protocol will be used to assess the quality of noise removal. Specific tasks will also be used to cause global blood flow changes. These include: Breath holding, Valsalva Maneuvers (breath hold while voluntarily blowing into a non-compliant tube), and other non-invasive ways to alter global blood flow. During scans we may collect other measures including heart rate traces, chest movement, non-invasive end-tidal CO₂, non-invasive blood pressure, galvanic skin response, and eye movements. Data will be collected with a wide range of fMRI scanning parameters to help distinguish signal sources. This includes T2*-weight BOLD imaging, arterial spin label, multi-echo imaging, and systematically varying voxel size, repetition time, and flip angle.

Outcome Measures:

The primary outcome measure for calibration and non-neural noise removal is increased precision of results across runs and subjects. Proper calibration should result in less response magnitude variation across volunteers in each brain region. Removal of temporal noise should result in resting connectivity measures that are less sensitive to draining veins.

Analysis Procedures:

Data will be analyzed using existing calibration methods as referenced above and new methods will be developed. New methods will focus on examining both temporal and frequency profiles of the data.

v. *Real time fMRI methods development (Bandettini)*

Experimental Procedures:

In this study subjects will participate in two sessions. In the initial session they will be trained to regulate the fMRI signal in a target region of their brain. In the return session, their retained ability will be evaluated and augmented with more training if necessary. Participants will undergo a functional localizer scan to identify a target region of interest (e.g., subjects may view

pictures or videos, or listen to sounds during the scan). They will then have several training scans (around 10 minutes each) where they will learn to up-regulate the region of interest using visual feedback of their brain activation from the regions determined in the localizer scan, alternating with periods of rest. They will then perform a transfer task identical to the training task but without feedback to determine whether they have learned to regulate the appropriate brain region. In the return session, they will perform the transfer task after the functional localizer, followed by a set of repeat training tasks.

Outcome Measures:

Participants will get direct feedback of their ability to regulate the target brain region. An increase in signal (correlation coefficient) will be used as an indicator of improved control of the target brain region. This value should increase over each of the training runs, be maintained in the transfer run and will possibly decrease somewhat in the return session.

Analysis Procedures:

Real-time analysis of the data will be performed using the in-house data acquisition computer running AFNI with real-time options. Signal from control regions, motion and physiological readings will be observed to ensure task compliance and data quality. After the experiments, each training run will be analyzed using AFNI, after standard preprocessing measures (motion correction, slice-timing, smoothing, transformation into standard space), the standard general linear model (3dDeconvolve) will be used to generate the correlation coefficients. The mean signal in the target regions will be trended over each of the training runs to evaluate whether the ability to regulate the region improves with training. Group analysis will be performed to identify which regions were commonly used to up-regulate the target regions or if obvious differences in strategies were used by different participants. The transfer and return run will be analyzed similarly and their results contrasted with the initial training.

vi. Long resting state scans for development of clustering methods (Bandettini)

Experimental Procedures:

A series of long functional scans (ranging from several minutes to about an hour long) with high spatial and temporal resolution will be collected to study the evolution of whole-brain connectivity patterns at different time scales ranging from a few seconds to several minutes. Three different experimental paradigms will be used: (1) resting-state scans in which subject will be asked to remain still and let their thoughts wonder freely; (2) naturalistic stimuli scans in which subjects will watch videos and/or listen to continuous auditory stimuli (e.g., music or short stories) for the whole duration of the scan; (3) combined-task scans in which a series of rest, naturalistic and typical task-based paradigms will be concatenated into a single scan so that subjects undergo different cognitive states (e.g., free thoughts, engage with a video presentation, perform a very specific task such as a working memory task or a language comprehension task, etc.). In addition to these functional scans, high-resolution anatomical scans will be acquired during each visit to the scanner. We plan to acquire data on both 3T and 7T systems. In addition to the fMRI data, we will also collect additional data at the scanner such as respiration, pulse, skin galvanic response and/or eye movement to aid in fMRI data pre-processing and interpretation.

Outcome Measures:

Correlation between fMRI data and additional behavioral data (e.g., eye tracking data, skin conductance data, and experimental paradigm events) will be the primary outcome measure.

Analysis Procedures:

In addition to traditional resting-state analysis procedures (e.g., seed-based and ICA-based analysis), we will also conduct correlation window analysis with several window sizes ranging from a few seconds to several minutes. For the connectivity analysis, nodes will be defined both anatomically—based on automatic parcellations generated with FreeSurfer—and functionally—based on localizer scans and functional atlas available online. Different clustering algorithms will be used to detect periods of time for which whole brain connectivity patterns are most similar. Reliability metrics will be computed to find the most reliable clusters and analysis approaches. Correlation between fMRI data and additional behavioral data (e.g., eye tracking data, skin conductance data, and experimental paradigm events) will be used to better understand how a given whole-brain connectivity pattern relates to a given cognitive state or physical act from the subject. Inter-subject BOLD time-series correlations for both naturalistic and combined-task scans will be computed to look for commonalities across subjects.

vii. *Improved diffusion imaging stability and distortion reduction (Bandettini)*

Experimental Procedures:

This experiment will be performed on both 3T and 7T. Subjects may participate in either or both scans. We will acquire multiple diffusion imaging scans by changing relevant scanning parameters in order to increase image stability and reduce distortion. Field maps will also be measured in some scans. Volunteers will be told to remain as still as possible during a 3T or 7T MRI scan. During each scanning series, brain volumes with the same field of view and voxel size will be repeatedly collected. Each volume will include a distinct diffusion gradient and diffusion direction. These volumes can be combined to calculate a diffusion tensor (Basser et al., 1994). Without noise, a diffusion tensor can be calculated with as few as 6 diffusion directions at a constant diffusion magnitude plus one volume with no diffusion weighing. Typically tensors are calculated on at least 25 volumes of data with different diffusion directions and constant magnitude plus several volumes with no diffusion weighting. It is possible to get probability distributions of tissue anisotropy using many more directions. For examples an early paper on high angular resolution diffusion-weighted imaging (HARDI) used 43 directions each repeated 20 times. (Frank, 2001) collected in 34 minutes. Diffusion spectrum imaging methods vary both the diffusion direction and magnitudes over hundreds of volumes to increase accuracy (Wedeen et al., 2005). For practical reasons, studies where volunteers are asked to keep their heads still rarely last longer than an hour and are often 20-30 minutes. The decisions on what to acquire during that time varies by study goal.

Outcome Measures:

For distortion correction, the key outcome measure will be how well anatomical landmarks in the diffusion images align with anatomical landmarks in less distorted volumes such as T1-weighted 1mm³ or smaller brain volumes. Where distortions cannot be completely removed, we will also examine whether spatial distortion is more similar across volumes with different directions or magnitudes. The key outcome measures will be the precision and accuracy of the diffusion measures. For example, are fractional anisotropy measures consistent across scans? If the same data is collected twice on the same person, are tractography results consistent? Do certain data collection and tractography methods more reliably connect brain areas that are expected to be connected and don't connect areas that should be connected based on anatomical knowledge? Does a change in a parameter, such as voxel size, significantly change results?

Analysis Procedures:

Data will be reconstructed from k-space using stock methods from the MRI scanners and in-house code. Preprocessing will include motion correction, eddy current distortion correction,

additional distortion corrections, and calculations of tensor or spectrum parameters using packages such as TORTOISE (Pierpaoli et al., 2010) and in-house code. DTI tracts will be calculated using both tensor-based (Mori et al., 1999), and probabilistic approaches (Chung et al., 2006).

viii. ***Can blood volume fMRI overcome limitations of BOLD fMRI? (Bandettini)***

Experimental Procedures:

Stimuli will include visual stimuli such as flickering checkerboards and short movies of moving body parts, and sensory stimuli such as vibration, touch, or air puffs produced using MRI-safe devices (no part of the device will contain any metal) with or without motor movements.

Participant responses will vary by task. For example, they might be asked to move their fingers while watching a video of fingers moving, or produce mental imagery of touch with and without movement. In some resting-state scans they might be asked to rest with eyes open or closed, and during some scans they might be asked to do the Valsalva breath hold (as in *study iv* above “calibration and non-neural noise removal”)

Outcome Measures:

aWe will measure participants cardiac and respiration curves, T1 and T2* MRI signal characteristics across time and space. fMRI signal changes will be investigated with respect to stability and spatial distribution of VASO and BOLD fMRI.

Analysis Procedures:

Participants behavioral data will be analyzed to estimate their performance. fMRI Data will be analyzed with established software packages, such as SPM, FSL, AFNI, ODIN, Freesurfer and custom designed C++, Python, and MATLAB programs.

ix. ***How do inherent beliefs and biases influence continuous processing during naturalistic tasks? (Bandettini)***

Experimental Procedures:

Participants will perform cognitive tasks where they may be asked to view video clips, often paired with associated audio, with durations ranging from a few seconds to several minutes. Stimuli are selected to vary in their levels of engagement and include continuous clips (e.g. animated shorts, short live action movie clips), as well as clips that present a series of information from different perspectives (e.g. debate style framework) on common social topics (e.g. Is social media good for society? Should electronic tablets replace textbooks in schools?). During these tasks, participants may be asked to focus or divert their attention to specific aspects of the audio/video clips. For any of the clips, participants may be asked to rate, evaluate, or verbally describe aspects of the stimuli. As participants perform these tasks, we will record behavioral, fMRI, MEG, EEG, eye tracking, and/or physiological data. After tasks in the scanner are completed, participants may be asked to complete additional behavioral tasks, for example a measure of personality, memory or vocabulary. Before, during and/or after stimulus viewing, participants may also be asked to answer a prompt designed to elicit free speech (for example, “Please retell the events in the movie in as much detail as you can remember”, or “Please give your impression of the events in the movie”). This speech will take place either outside the MRI scanner or inside the scanner using an MR-compatible noise-canceling microphone and will be recorded. However, this speech is not expected to contain any identifying or protected health information about the participant, and in the event that a participant inadvertently includes identifying and/or PHI in his or her speech, that segment of the audio recording will be destroyed as soon as possible and will not be analyzed. Subjects may also be implicitly or explicitly primed using techniques such as subconscious

priming (e.g., presentation of a brief stimulus below the conscious detection threshold prior to start of the main stimulus), mood induction (e.g., subjects are asked to produce or engage with content of a certain emotional valence before viewing the main stimulus), order and repetition effects, or other approaches.

Outcome Measures:

The outcome measures for this study include reaction times, behavioral performance, neuropsychological assessments, physiological measures (e.g. heart rate, respiration, galvanic skin response), eye tracking, speech analysis, and brain activity (fMRI, EEG, MEG).

Analysis Procedures:

The outcome measures will be combined and analyzed using classifiers and other multivariate techniques to uncover patterned differences in behavior, brain activity, eye movements, and physiological measures related to the stimulus engagement, as well as individual task performance. Univariate analyses will be also conducted to analyze the relationship between BOLD activity (in fMRI) and EEG/MEG signal. Multivariate analyses (e.g. partial least squares) will be used to link data from these different imaging technologies together.

x. *Relationship between BOLD and on-going cognition with and without tasks (Bandettini)*

Experimental Procedures:

We will conduct a series of resting-state and task-based functional scans during which subjects will be prompted to describe the content of their mental experience via an auditory and/or visual cue. This will occur multiple times during each scan. The timing of these cues to share their inner experience (i.e., thoughts, mood and sensations) may be pre-defined, random, may depend on real-time analyses of the incoming fMRI, EEG, eye tracking, or other acquired data, or at times defined without any real-time information.

Following each prompt, subjects will have the opportunity to describe their inner experience in the moments preceding the cue in two different ways. Subjects may be asked to vocally describe their experience and these descriptions may be recorded with an MRI compatible microphone. In addition, subjects may be presented with a series of questions on the screen that will help to better elucidate the nature, content, and timing of their on-going cognition at the time of the prompt (e.g., “How alert were you?”, “Was your on-going experience happening spontaneously or under deliberate control?”). Subjects will respond to these questions using a suitable MRI compatible subject response equipment (e.g., an MRI compatible response box or joystick). At the beginning of each prompt, subjects will be given the option to discard a prompt should they rather not share the content of their on-going cognition at that particular time. During the experiment, we may also acquire concurrent measures of body and facial motion (e.g., using electromyography and video recordings) to get a full picture of the mental, motor and emotional state of subjects while being scanned.

Completion of this experiment may require several visits. One visit may be used to explain the goals and logistics of the experiment to the subject, and also to instruct them on how to accurately report the contents of their on-going cognition/mental state in the moments prior to the prompt using both the oral description and the answers to the on-screen questionnaires. Subjects will be told that they can decide to not answer any or all of our questions at any moment. Once subjects acknowledge that they understand the logistics of the experiment, we may conduct a series of mock training runs outside the scanner. Subjects will fixate on a crosshair on a computer screen and be prompted to share a description of their on-going cognition at discrete moments. At the end of each run, the experimenter will discuss the responses with the subjects to help improve their

ability to reflect and share their on-going mental activities. Previous research suggests that such training sessions help subjects provide more accurate descriptions of their mental activities.

Subjects may participate in multiple MRI scanning sessions for each task. Each of these visits may start with a reminder of the experiment logistics. Following that, subjects will enter the MRI scanner. A series of anatomical and functional scans will be conducted, during which subjects may either rest or perform tasks. In addition, they may be prompted to share their on-going cognitive activities at multiple moments during the scans. We may also add cognitive tasks to bias a participant's mental state such as using a reward task to raise or lower mood. Any monetary reward that a subject receives will be added to the total compensation for the visit. As in previous experiments, we may record additional signals while inside the scanner (e.g., cardiac, respiration, eye tracking, EEG, galvanic skin response, electromyography and video recordings of facial expressions and body motion). Once outside the scanner, the experimenter may have a short discussion about their reported experiences in a manner similar to that in a training visit.

Outcomes Measures:

These may include models describing the relationship between fMRI derivatives (e.g., activity maps, static functional connectivity, dynamic functional connectivity), other measures (e.g., EEG, eye tracking, galvanic skin response, electromyography, facial expressions, motion events), and concurrent reports of covert on-going mental activities. Additionally, we will generate novel analytical techniques that will permit others to capture, characterize and (if needed) remove the contribution of such experimentally uncontrolled cognitive processes to fMRI recordings.

Analytical Procedures:

In addition to traditional task and rest analysis procedures (e.g., general linear models, seed-based and ICA-based connectivity analyses), we will also perform additional analyses based on metrics of dynamic functional connectivity (e.g., sliding window correlations, co-activation pattern analysis, quasi-periodic patterns, connectivity gradients, graph theory metrics). Activity and connectivity patterns, in parallel with different aspects of subjects' descriptions of their on-going mental and motor activities, will be input to advanced machine-learning models to help model the relationship between these two variables—such as fMRI data and reports of mental activities. These will include, but are not limited to: clustering, dimensionality reduction, classification, and regression methods. The goal here is to be able to capture complex relationships that cannot be captured using simpler models.

f. End of Participation

At the end of every experiment subjects will be debriefed and compensated for taking part in the experiment. Results from the study will not be shared with participants.

Incidental Findings: Subjects will be informed about any finding that may require further evaluation or care. No evaluation or treatment for these conditions will be provided at NIH. If needed, the subject will be referred to a health care provider. We may not inform the subject about minor abnormalities that do not have importance for his/her health or well-being.

5. Management of data and samples

a. Data storage

Behavioral measures such as RT and percent correct values and structural and functional MRI data will be stored on password protected LBC computers. After every scanning and behavioral session, all data collected will be securely transferred to secure lab servers. These lab servers are secured in the LBC server room. All questionnaires and forms completed by the subjects will be

securely kept in the lab in a locked drawer. The lab is locked when not occupied. Only researchers named on this protocol and their research assistants will have access to this data. After every scanning session, all data collected will be securely transferred from the NIH MRI Research Facility (NMRF) and MEG facility computers to secure lab servers.

b. Data sharing plan

This protocol is not subject to the Genomic Data Sharing (GDS) policy. No samples are stored or shared. Data may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data from this protocol may be open-access or restricted access.

Data will be stripped of identifiers and may be coded (“de-identified”) or unlinked from an identifying code (“anonymized”). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

Re-consent will be obtained prior to sharing from participants whose data were collected prior to the implementation of Amendment PP, if consent was not previously obtained.

6. Additional Considerations

a. Research with investigational drugs or devices

N/A

b. Gene Therapy

N/A

7. Risks and discomforts

a. History, physical and neurological examination

The risks and discomforts of the screening and baseline evaluations are minimal. No discomfort is expected to be associated with the physical examination or the clinical interview. Subjects may potentially feel uncomfortable when asked personal questions.

b. Neuropsychological tests and Questionnaires

There is no medical risk from taking neuropsychological tests. The tests may be fatiguing and boring. Short breaks will be given during the testing at regular intervals, and if the subject expresses fatigue. Subjects may find some questions embarrassing or anxiety provoking. Subjects may refuse study participation at any time.

c. Behavioral Tasks

There is no medical risk from performing behavioral tasks in this protocol. All tasks are non-invasive and will be completed by staff trained to complete these procedures. No discomfort is expected. Subjects may refuse study participation at any time.

d. IAPS

In some experiments subjects may be shown images containing emotional material, such as a picture of a ferocious dog. If a subject finds viewing these pictures distressing and wishes not to participate, they will be withdrawn from the experiment.

e. Unpleasant Sounds:

Some sounds subjects will hear are intended to produce strong positive or negative emotional responses, and may include aversive tones and distress sounds. If subjects find these sounds distressing, and wish not to participate, they will be withdrawn from the experiment.

f. Physiological Monitoring

None of the physiological monitoring techniques is invasive or poses any known risks. When electrodes are attached to the skin, some subjects may experience some discomfort and the conductive gel may sometimes causes mild skin irritation.

g. Eye tracking

None of the eye movement monitoring techniques is invasive or poses any known risks.

h. MRI (including sMRI and fMRI)

MRI is widely regarded as a safe, noninvasive procedure for visualization of brain tissue in both adults and children. People with claustrophobia may find this procedure uncomfortable as it involves having one's head confined to a relatively small space. Approximately 3% of non-sedated patients cannot tolerate the procedure because of claustrophobia. There may be mild muscle stiffness and fatigue. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing. If a subject is known to have hearing loss, the research MRI scan will not be performed. All subjects that undergo a research MRI scan will be fitted with hearing protection. All subjects will be asked to complete an MRI screening form prior to each MRI scan. There are no known long-term risks of MRI scans.

Steps taken to minimize risk during MRI:

Potential risks associated with MRI scanning will be minimized in the following manner:

- Claustrophobia from MRI will be reduced by explaining the nature of the procedure in detail prior to their enrollment. Subjects will be told that they can interrupt the procedure at any time and be removed from the scanner chamber by pressing a call button that they will hold during the entire procedure; they will be informed that they will be able to communicate back and forth with the experimenter via an intercom system.
- As specified in the exclusion criteria, subjects with cochlear implants, implanted brain stimulators, aneurysm clips or other metal in the head (except the mouth), as well subjects with implanted medication pumps, pacemakers, intracardiac lines, significant heart disease, or pregnancy will be excluded from MRI studies.
- Although the risk of MRI scanning in pregnancy is not known, and there is no indication that MRI poses any danger to a fetus, all female subjects of child-bearing potential will be given a

pregnancy test within 24 hours prior to the scheduled MRI scan. If the test is positive, the scan will not be done.

i. 7T MRI

The FDA has determined that there is no significant risk associated with the 7 tesla MRI for adults (<http://www.fda.gov/cdrh/ode/guidance/793.pdf>). Since 7T MRI is not FDA approved for research purposes, it is considered investigational and subject to IDE requirements for a Non-significant Risk (NSR) device.

Most people do not have any ill effects from the strong magnetic field, but some people experience brief periods of muscle twitching, eye discomfort, dizziness, mild nausea, headache, a metallic taste in their mouth or a sensation of flashing lights. Many of these result from moving too rapidly in the magnetic field. Subjects will be instructed to walk slowly to the MRI table. Once on the table, we will secure his/her head with cushions to prevent the head from moving. There is no evidence that scanning at high magnetic field strengths is dangerous, but the long-term effects of using 7 Tesla scanners is not known. All scanning under this protocol is performed in a manner consistent with the FDA's safe operational limits. FDA approved hardware safety measures are operational during scanning so that FDA guidelines are not exceeded. The FDA considers these research scans to be Non-significant Risk (NSR) since they do not present a potential for risk to the health, safety, and welfare of a subject.

Steps taken to minimize risk during MRI:

- In order to minimize the occurrence of high field related sensations while scanning on the 7T scanner, subjects will be instructed to move slowly while in the scan room, and the table on the 7T scanner moves significantly slower than those in the 3T scanners.
- The subject can ask to stop the scan at any time if he/she feels uncomfortable.

j. MEG

MEG passively records neural activity and therefore there are no physiological effects of MEG scanning. Similar to MRI procedures, there may be a small amount of discomfort from having to remain as still as possible for the 20-90 minutes usually required for each of the MEG scans which may result in mild muscle stiffness and fatigue. There are no known long-term risks of MEG scans. The CTF Omega 2000 system (or similar) will be used for MEG recordings. This device is FDA approved, and will be used in a manner consistent with the FDA's safe operational limits.

k. EEG

There is minimal risk from standard EEG, EEG combined with MEG, or from the addition of EEG to the MR scan as the cap and system used is fully MR compatible. The electrode cap may be uncomfortably tight, or there may be pressure points at the back of the head from pressure on the scalp from lying on the cap during the scan. These issues can be mitigated by getting the subject's feedback after the cap is put on and by using appropriate supportive padding during the session/scan. Some subjects may experience mild skin irritation at the electrode locations from several factors including pressure from the electrode itself, or lack of air exposure to the skin. This skin irritation disappears quickly after the removal of the EEG cap.

l. Electric Shock:

The electric shocks that a subject will receive are intended to make him/her anxious. They are not dangerous. We will find a level of intensity that is unpleasant, but not painful. If a subject

finds the shocks painful, he/she is free to stop the experiment and withdraw from the study at any time.

m. Taste Testing:

There is minimal risk or discomfort from ingesting the small amounts of liquid that are used for studies involving taste testing.

8. Subject safety monitoring

All subjects will be instructed about, and receive practice with, each test before they begin to perform it and, before a test is formally administered, adequate comprehension of the instructions for each test will be insured by the test examiner.

During an assessment, a study investigator or a research assistant working with the study investigator, will usually be in the room with the subject or in the room just outside of the MRI scanner room. Study staff will monitor individuals during participation and subjects will be encouraged to tell experimenters of any discomfort. If apparatus cannot be adjusted to relieve discomfort, the experiment will be stopped. Subjects may withdraw at any time.

During MRI scanning, subjects will be given a call button and instructed to use it in case of emergency or if the subject feels any discomfort in the scanner. Throughout the scan session verbal contact with the subject will be maintained from the control room via an intercom device.

9. Outcome measures

a. Primary outcome measures

Specific primary and secondary outcome measures for each experiment have been outlined in the study objectives section for clarity.

In general, for behavioral experiments, reaction time and accuracy on a task will be the main measures. In addition, signal detection theory measures such as d' (d-prime) and decision criterion may also be computed.

For fMRI experiments, BOLD percent signal change will be the primary outcome measure.

10. Statistical Analysis

a. Analysis of data/ study outcomes

Resting-State Data: Preprocessing and de-noising

The goal of preprocessing resting connectivity data is to increase the likelihood that connectivity measures are based on neural activity of known brain regions rather than subject motion, breathing, or MRI scanner noise. There are several general steps in data processing, but most studies try multiple methods for many steps to make sure results aren't caused by data

preprocessing decisions. Data are processed using software like AFNI (Cox, 1996). Much of preprocessing can be divided into registration and denoising.

Registration: Alignment of functional and anatomical images is needed to increase accuracy of anatomical localization (Saad et al., 2009). AFNI cross-modal registration software will be used to align anatomical images for each subject to the RS-EPI time series (Saad et al., 2009). Aligned anatomical images will then be processed using the FreeSurfer automated pipeline for generating cortical surface models and whole brain segmentation (Fischl et al., 2002). Using AFNI's suite of programs (Cox, 1996; Cox, 2011), individual cortical surfaces are geometrically corrected, standardized, and registered to the cortical surfaces of the N27 template brain (Holmes et al., 1998) by SUMA to ensure that the N27 template corresponds with individual cortical surfaces (Argall et al., 2006; Saad and Reynolds, 2011; Saad, 2004).

De-noising: This usually includes correcting for subject movement over the time of the fMRI runs. It can also include approaches like the ANATICOR method, which uses regression to remove recorded nuisance physiological signals such as cardiac and respiratory signals, as well as head coil/hardware artifacts (Jo et al., 2010). Other approaches use independent component analysis for de-noising (Beall and Lowe, 2010; Starck et al., 2010), or remove volumes with increased subject motion (Power et al., 2012). Additional 1-TR delayed regressors of the nuisance variables are also sometimes included in order to remove any additional delayed effects of noise sources (as in (Buckner et al., 2009; Fox et al., 2005)).

FMRI data preprocessing and analysis

Analyses of MRI data will be carried out using AFNI's suite of programs (Cox, 1996; Cox, 2011). Structural scans (either SPGR or MP-RAGE) will be used to provide high-resolution information about the location of active brain regions. AFNI cross-modal registration software will be used to align anatomical images for each subject the EPI time series (Saad et al., 2009). For some experiments, aligned anatomical images will be processed with FreeSurfer's automated pipeline for generating cortical surface models and whole brain segmentation (Fischl et al., 2002). The structural information in an MRI scan can also be used to warp an individual scan to the size and shape of a template or atlas brain space (Evans et al. 1991).

Changes in the MR signal observed in the functional scan series provide information about BOLD activation in cortical and subcortical brain regions. A whole brain volume is typically acquired every 1-4 seconds, while each imaging run typically lasts between 4 and 8 minutes, with data acquisition occurring continuously. Subjects typically perform 5-12 runs during a single experimental session. Thus, data from all runs will be combined into a single file containing on the order of 1,000 brain volumes. To correct for subject motion over the course of the experimental session, all of the brain volumes will be aligned to the volume acquired closest in time to structural scan (either the first or the last volume depending on whether structural scans were collected at the beginning or end of the experimental session) (Cox et al. 1999). Then, all brain volumes will be blurred with a Gaussian filter of the same dimension as the voxel size (usually 4-8 mm). Finally, multiple linear regression will be performed on the collected data in order to, first, find all brain areas in which the MR signal varies with the behavioral stimulus and task performed by the subject; and second, to estimate the magnitude of the response in active brain areas.

Multiple regression is performed in one of two different ways, depending on the experimental design. In the first type of experimental design, stimuli of the same type are blocked together, leading to the name "block design". These blocks typically last 20-60 seconds,

and are separated by rest intervals in which the subject does not perform an active task (usually simply fixating a crosshair or viewing a blank screen). Within a given scan series or fMRI run (which typically last 3-8 minutes) subjects alternate between rest and different experimental conditions in an interleaved or random fashion (e.g. block of pictures of faces; long rest; block of pictures of houses; long rest; etc.) In the second type of experimental design, the so-called rapid event-related design, single stimuli are presented, followed by randomly varying (but usually short) fixation intervals (e.g. face picture; 2 sec rest; house picture; 4 sec rest; house picture; etc.).

For both experimental designs, a number of regressors of no interest will be included in the analysis to account for variance in the MR time series: a second-order polynomial will be included for each run to account for shifts in the baseline, and linear or slow second-drifts in the signal within each run; and the motion parameters calculated by the motion correction procedure. The regressors of interest differ for the two types of designs. In order to analyze block design experiments, a single regressor will be created for each stimulus type (e.g. one regressor for houses, one for faces) which is positive when that stimulus is presented and zero everywhere else. These regressors will be convolved with a synthetic hemodynamic response function (typically a gamma function) which smoothes and shifts the regressor to make it better match the smooth, time-delayed hemodynamic response to the behavioral stimulus. These regressors of interest (and the regressors of no interest) will be fit to the time series of each voxel in the brain, separately. An F-statistic will be calculated for the variance accounted for by all regressors of interest, and this will be used to threshold the activation maps, showing active brain areas. The beta-weight, or amplitude, of each regressor provides an estimate of the amplitude of the response in each voxel.

In order to analyze rapid event-related experiments, multiple regressors will be created for each stimulus type. For each stimulus type, a separate regressor will be made for each time point in the estimated response. For example, to estimate the response to a face stimulus with 1-second resolution in a 15-second window, 15 time shifted regressors will be created, each modeling the response at a given peri-stimulus time. With two stimulus types, this would result in 30 regressors of interest which will be then fit (along with the regressors of no interest) to the time series of each brain voxel. The full-F statistic of all of the regressors of interest will allow determination of active brain areas. The amplitude or beta-weight of the individual delta-function regressors can be plotted in order to determine that amplitude, width and latency of the hemodynamic response to each stimulus type.

To create summary results, regions of interest corresponding to anatomical structures will be drawn on the high-resolution anatomical image. Then, active voxels within these regions will have their amplitudes of activation averaged together to provide a representative measure for the entire brain region. To create average activation maps, datasets will be converted to standardized Talairach space (Talairach and Tournoux, 1988). Then, an ANOVA will be performed for each voxel across subjects to determine if the amplitude is significantly different from zero, or if it differs across subjects. The results will be displayed on an average anatomical dataset or a representative individual subject dataset.

Multi-voxel Pattern analysis:

To obtain input features for the MVPA, we will use a general linear model (GLM) to estimate each subject's fMRI responses to every individual stimulus presentation. We use the term *sample* to refer to one such estimate. To perform the MVPA, within each ROI the N samples for each condition pair in an Experiment – for example, the N samples for presentations

of wedges on the upper and lower right – will be conceptually represented as points in an D-dimensional space, where D is the number of features (nodes in the ROI). Support vector machines (SVM) will identify the hyperplane that optimally divided the points into groups by maximizing the margin between two groups; in this example, the groups would be upper vs. lower right. The term *training* refers to this process. During training, one sample will be left out (the leave one out cross-validation, LOOCV, method). The sign of the distance between the left-out sample and the hyperplane will be used to determine the class of the left-out data. The prediction will be compared with the real left-out data to yield a single binary measurement: is the prediction correct or not? During cross-validation, the whole procedure will be repeated N times such that every sample was left out once, thus obtaining many binary measurements of prediction accuracy. Within each subject the ratio of correct to total predictions will be calculated, producing an individual *percent correct* measurement. The individual percent correct measurements will be averaged across subjects to obtain an overall percent correct for (in this example) upper vs. lower right selectivity.

MEG Data Analysis

MEG data will be collected at 600Hz using a 275-channel whole-head MEG system (CTF Omega 2000) operating in a shielded environment. Background activity will be subtracted using online 3rd gradient formation. Data collected in the MEG facility will first be securely transferred to LBC computers. Each subject's MEG data will be analyzed in the following ways:

1. Analysis of temporal characteristics of magnetic fields
Standard MEG data analysis techniques including event-locked averaging will be performed using the software package provided by CTF.
2. Synthetic Aperture Magnetometry (SAM) to perform localization of magnetic field sources.
SAM analyses will be performed using CTF and AFNI software. Each subject's SAM volumes will first be converted to z-scores to eliminate inter-subject variability in relative power levels, and transformed into Talairach space. The Talairached volumes for each epoch or event of interest will then be averaged and subjected to a 3D t-test to identify regions that are significantly active. SAM volumes will also be computed for a series of paired, overlapping, temporal windows, for specific conditions of interest. Power ratios between corresponding time windows, will be used to obtain a time-series of activation for each voxel. Statistical tests will be performed on the resulting datasets to identify regions that respond significantly to specific events related to the task. Resulting maps will be displayed on an average anatomical dataset in AFNI.
In addition we may use other new methods of analysis developed by us or the MEG Core Facility as and when that occurs.

EEG Data Analysis

The MR magnetic field and imaging gradients induce artifacts in the EEG signal when it is recorded during an MR scan. Thus, simultaneous EEG-fMRI data will be processed to remove gradient artifacts (induced by the imaging gradients) and cardio-ballistographic artifacts (induced by the subject's beating heart in the magnetic field) using standard techniques. The cleaned EEG data will then be analyzed using time-frequency plots and coherence measures, sliding window measurements of oscillatory power changes and other methods as appropriate. (We will also perform analyses which will necessitate including the simultaneous EEG-fMRI data and explore whether changes in resting-state fMRI signal fluctuations are related to changes in electrophysiological events.)

b. Power analysis

Power is the percentage chance of detecting a certain size difference between conditions given a particular sample size, variability, and required p-value. The variability is difficult to predict a priori, but the literature does provide us with some guidance.

Most of the experiments will be conducted in two phases. In a pilot phase, 10-15 subjects will first be tested. Depending on the effect size seen in this initial phase, a further 20-25 subjects will be recruited. In general, 30-40 subjects will be recruited for each experiment. This is consistent with other behavioral, fMRI, MEG and EEG studies in the literature that have adopted similar experimental designs.

Our accrual ceiling is currently at 4100. We anticipate that based on the number of experiments concurrently ongoing, we will accrue about 150-250 subjects per year. If subjects withdraw from an experiment they will be replaced.

11.Human Subjects Protection

a. Subject selection

Rationale for Selection if not equitable:

Subject selections will be equitable among those individuals who meet the inclusion criteria. Every effort will be made to balance for gender and race. We will not test subjects greater than 65 years of age because it is not clear how the effects of aging may impact on our hypotheses concerning the neural pathways involved in the different aspects of cognition and perception.

b. Justification for Exclusion of Children

Our proposed set of experiments is designed to test various aspects of adult human brain function. We know from studies in developmental neuroscience that the functional organization of the developing brain is different from that of the adult brain. Therefore children under 18 will be excluded from the protocol.

c. Justification for Exclusion of Other Vulnerable Subjects

We will not enroll cognitively impaired or mentally ill subjects into the protocol, as their brains may perform cognitive and perceptual tasks differently than healthy subjects.

d. Justification of Sensitive Procedures

Not applicable.

e. Safeguards for Vulnerable Populations

For all MRI experiments, pregnant women will be excluded from participation due to the unknown effects of high magnetic field (Nagayama et al., 2002) on a developing fetus. Women of childbearing age will undergo a pregnancy test within 24 hours prior to any MRI.

Protections for NIH employees and staff participating in this study include 1) assuring that the participation or refusal to participate will have no effect, either beneficial or adverse, on the subject's employment or position at the NIH, 2) giving employees and staff who are interested in participating the "NIH Information Sheet on Employee Research Participation" prior to obtaining consent, and 3) assuring that there will be no direct solicitation of employees or staff.

This study collects sensitive information on medical and psychiatric diagnoses and drug and alcohol use. The PI will train study staff regarding obtaining and handling potentially sensitive and private information about NIH employees through staff discussions and written branch/section procedures. Prior to enrollment, potential participants will be informed that this sensitive information will be in their NIH medical record.

12.Consent documents and process

a. Designation of those obtaining consent

Study investigators designated as able to obtain consent in section 11g above, will obtain informed consent from participants. Consent for NIH employees will not be obtained by coworkers.

b. Consent procedures

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. A copy of the consent signed by the participant, witness and investigator will be given to the participant. The original will be filed in the medical record. A copy of the signed consent form will be securely stored in the LBC in a locked drawer in a room that is locked when not occupied.

If consent was not obtained for broad sharing of data under the original consent, written consent will be obtained via mail and telephone contact. A letter (see Appendix 25G) will be mailed/Faxed/e-mailed to them along with two copies of the consent. The letter will be followed by a phone call to assess interest. If the participant is interested, a time will be arranged when a witness can be present on their end to go over the consent and answer questions. The potential participant will be instructed to sign and date one copy of the consent and have the witness also sign and date. The signed consent will be e-mailed, Faxed or mailed back to the investigators in a prepaid envelope, and the participant will keep the other copy. The investigator who participated in the consent process will then sign the consent and a copy with all three signatures will be sent to the participant. To protect confidentiality during fax correspondence, a NIH fax coversheet will be used. The consent will be submitted to a non-public/non-common use fax machine where only the PI or designee has access to incoming faxes. The patient must be able to securely receive a fax on their end.

c. Consent documents

The consent form contains all the required elements. A single consent form is used for all healthy volunteers participating in any of the behavioral, MRI or MEG experiments listed under this protocol.

d. Waiver of consent for sub-study: “Using naturalistic and dynamic memory stimuli to investigate how the brain represents episodic memories over time”

Usage of video clips provided by participants in the sub-study listed here will be done under a waiver of informed consent for people who are visible in these video clips. The waiver of consent meets the criteria set out in 45 CFR 46.116(d):

- The research involves no more than minimal risk to the subjects. The sharing and additional use of data does not present more than minimal risks to participants.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the waiver or alteration.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation. However, these data will be unlinked, and the identities of the participants will not be traceable, therefore no later information can be provided.

13. Data and Safety monitoring process

a. Data and Safety monitor

The principal investigator (Dr. Martin) is the primary responsible party for data and safety monitoring.

b. Data and safety monitoring plan

The PI will review data and safety parameters at least annually. The PI will document the data and safety review in the research records and at the time of continuing review.

c. Criteria for stopping the study or suspending enrollment or procedures

The study (or the study/specific procedure) will be stopped if there is any Serious Adverse Event related to the research.

The PI and IRB will determine if changes are needed for the research to continue or if it will be closed. Any changes required as conditions for resuming the research must be submitted as an amendment and IRB-approved before the changes can be implemented.

14. Quality Assurance

a. Quality assurance monitor

Quality assurance will be monitored by the PI, the research team and the NIMH Office of Regulatory Compliance (ORO).

b. Quality assurance plan

As per ICH-GCP 5.18 clinical protocols are required to be adequately monitored. Monitoring for the NIH site will be conducted according to the “NIMH Intramural Program Guidelines for Monitoring of Clinical Trials”. Monitors under contract to the NIMH OCD ORO will visit the NIH site to monitor aspects of the study in accordance with the appropriate regulations, policies and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information from clinical databases (e.g. CTDB) with individual subjects’ records and source documents (subjects’ charts, laboratory analyses and test results, physicians’ progress notes, nurses’ notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors

also will inspect the clinical site study files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), NIH , and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, clinical database records and pertinent hospital/sources or clinical records readily available for inspection by the local IRB, OHRP, the site monitors, as applicable and the NIMH staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and applicable regulatory obligations.

15. Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations

Reportable events for this protocol will be tracked and reported in compliance with Policy 801.

16. Privacy

All research activities will be conducted in as private a setting as possible.

17. Alternatives to participation

Subjects do not receive any treatment in this study or forego any treatment in order to participate in this study. The alternative, therefore, is not to participate.

18. Confidentiality

Experimental data will be de-identified and coded. Data will be kept in NIMH encrypted password-protected computers. Data hard copies and keys to subject identity will be kept in locked cabinets in rooms that are locked when not occupied. Only study investigators and their research assistants will have access to electronic and hard copy data. The information gathered during this study will be kept confidential to the extent that the law allows. This study collects sensitive medical information. The PI will train study staff regarding obtaining and handling potentially sensitive and private information about NIH employees through staff discussions and written branch/section procedures.

19. Conflict of Interest

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report.

20. Technology Transfer

N/A

21. Research and Travel Compensation

Volunteers and patients will be compensated for time and research-related inconveniences.

Volunteers will receive payment in accordance with the inconvenience unit system of the Healthy volunteer Program, NIH. The compensation proposed is as follows.

Screening/History & Physical/Consent visit:

For a screening/history & physical/consent visit: \$30

NOTE: Volunteers who do not need a History & Physical (such as those screened under 17-M-0181) will receive \$30 for the consent visit.

Neuropsychological and Behavioral testing:

For the first hour or part thereof: \$20

For each additional hour or part thereof: \$10

Maximum (for a three hour session): \$40

Plus: \$10 for any discomfort associated with cognitive testing.

Total: \$50 maximum per session

MRI, MEG and EEG testing:

For the first hour or part thereof: \$20

For each additional hour or part thereof: \$10

Maximum (for a three hour session): \$40

Plus: \$70 for any discomfort associated with EEG and being in the MRI or MEG scanner

Plus: \$10 if the EEG is simultaneous with MRI or MEG

Total: \$110 maximum per session (for MRI, MEG and EEG) and \$120 for simultaneous EEG-fMRI or EEG-MEG

Female subjects who undergo a pregnancy test will be compensated \$20 for the inconvenience of providing a urine sample.

Subjects will receive a pro-rated amount for completed portions if they do not complete the experiment.

If for some scheduling or technical reason, a subject arrives for a visit, and we are unable to scan or test the subject, he/she will be paid \$20 for his/her time.

Subjects will be mailed a check at the end of each testing session.

If subjects earn money as part of tasks that included reward, this amount will be added to the total for that particular visit.

Reimbursement for travel will be provided for the memory sub-study in accordance with NIH guidelines. Employees and staff who participate during work hours must have permission from their supervisor. NIH employees must either participate outside of work hours or take leave in order to receive compensation.

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23. Attachments/Appendices

A. Participant Eligibility Checklist

To be considered for participation in the protocol, individuals must meet the following eligibility criteria.

	Inclusion Criteria	Yes	No
1.	Age 18 – 65 years?		
2.	In good physical health?		
3.	At least high school education?		

	Exclusion Criteria	Yes	No
1.	NIMH employee or relative?		
2.	Major medical illness?		
3.	Neurological illness?		
4.	Psychiatric illness?		
5.	Serious head injury?		
6.	Learning disability?		
7.	History of drug or alcohol abuse or dependence in past 3 months?		
8.	Prescription drugs or supplements affecting brain function?		
9.	Serious vision or hearing problem?		
Additional Criteria for MRI:			
9.	Pregnant?		
10.	Metal in body?		
11.	Unable to lie on back for up to 3 hours?		

B. Participant Screening Checklist

93-M-0170

At every visit, participants must meet the following criteria prior to participation in a study procedure.

Participant Name: _____ Date of Visit: _____

Investigator: _____ Research Assistant: _____

	Screening Procedure	Yes	No
For new participant:			
1.	Meets Inclusion/Exclusion criteria via phone screen?		
2.	History and Physical complete?		
3.	Consented to Protocol?		
4.	Added to Protocol in CRIS?		
5.	Qualifies for Behavioral experiments?		
6.	If MRI, NMR Safety Screening?		
	a. Qualifies for MRI experiments?		
	b. Qualifies for 7T scanning?		
	c. Clinical Scan < 1 year? (If No, scan must be MRI Brain Clinical Scan)		
	d. Normal brain scan results confirmed in CRIS?		
For returning participant:			
1.	History and Physical < 1 year?		
2.	Consent confirmed in CRIS?		
3.	Needs to be consented again?		
4.	Qualifies for Behavioral experiments?		
5.	If MRI, NMR Safety Screening?		
	a. Qualifies for MRI experiments?		
	b. Qualifies for 7T scanning?		
	c. Clinical Scan < 1 year? (If No, scan must be MRI Brain Clinical Scan)		
	d. Normal brain scan results confirmed in CRIS?		

C. Recruiting Materials

1. Text for all Studies:

Text for email advertisement:

You are receiving this message because your email address is included in the above listserv for NIH IRTAs or ClubPCR, the Yahoo! group for NIH IRTAs. The purpose of this message is to inform you of NIMH studies that are recruiting subjects. The moderator of the listserv/mailling list has permitted its use for this distribution. Please do not reply on this forum. If interested, please use the contact information listed below.

The Laboratory of Brain and Cognition at NIMH is recruiting healthy volunteers for a research study (#93-M-0170) looking at cognitive function. Tasks may include cognitive tasks, personality tests, magnetic resonance imaging (MRI), magnetoencephalography (MEG) and electroencephalography (EEG). Participants may choose what they would like to participate in depending upon their eligibility.

You may qualify if:

- You are between the ages of 18 and 65
- You have a high school education
- You are in good physical health

You may NOT qualify if:

- You are an NIMH employee or a relative
- You have current or a history of major medical, neurological or psychiatric illness
- You have had a serious head injury
- You have a learning disability
- You have a history of drug or alcohol abuse or dependence in the past 3 months, except nicotine
- You are taking medications or supplements that may affect brain function
- You have serious vision or hearing problems

You may not qualify for MRI studies under this protocol if:

- You are pregnant or believe you might be pregnant
- You have metal in your body (e.g. metal rods, plates or screws in the body or mouth, pacemakers, ear implants)
- You cannot lie flat on your back for up to 3 hours

Participation is free of charge, and participants are compensated for their time. The research study takes place in the Clinical Center on the NIH campus in Bethesda, MD.

If you are interested in participating, please contact:

NIMH Lab of Brain and Cognition, NIMHLBCVolunteer@mail.nih.gov, 301-827-5157

<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

Join A Study Website

Category: Adults/Healthy Volunteers

Title: Brain & Cognition Research Study

Researchers are enrolling healthy volunteers for an outpatient research study to learn more about how the brain works.

Research participation may include cognitive tasks, personality tests, brain imaging and/or magnetoencephalography (MEG) and electroencephalography (EEG). Participants may choose which research tasks they would like to participate in, which determines the number of visits (1-12) to the NIH Clinical Center in Bethesda, MD.

The study is enrolling eligible participants, between the ages of 18 and 65, who are in good physical health, and at least a high school education. There is no cost to participate and compensation is provided.

Contacts:

NIMH Lab of Brain and Cognition, NIMHLBCVolunteer@mail.nih.gov, 301-827-5157

Principal Investigator: Alex Martin, Ph.D.

Protocol #: 93-M-0170

Listserv (or Research Match, or craigslist)

Disclaimer: You are receiving this message because your email address is included in the above [insert listserv or mailing list]. The purpose of this message is to inform you of NIMH studies that are recruiting subjects. The moderator of the listserv/ mailing list has permitted its use for this distribution.

Join an NIH Brain & Cognition Research Study

Researchers are enrolling healthy volunteers for an outpatient research study to learn more about how the brain works.

Research participation may include cognitive tasks, personality tests, brain imaging and/or magnetoencephalography (MEG) and electroencephalography (EEG). Participants may choose which research tasks they would like to participate in, which determines the number of visits (1-12) to the NIH Clinical Center in Bethesda, MD.

The study is enrolling eligible participants, between the ages of 18 and 65, who are in good physical health, and at least a high school education. There is no cost to participate and compensation is provided.

Contacts:

NIMH Lab of Brain and Cognition, NIMHLBCVolunteer@mail.nih.gov, 301-827-5157

<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

Short Text

NIH Brain & Cognition Research Study

Join an outpatient research study enrolling healthy volunteers to help scientists learn more about how the brain works. Participation may include cognitive tasks, personality tests, brain imaging and/or magnetoencephalography (MEG) and electroencephalography (EEG). Adults ages 18 to 65, in good physical health, and at least a high school education may be eligible to participate. There is no cost to participate and compensation is provided. The study is conducted at the NIH Clinical Center in Bethesda, MD.

If you are interested in participating, please contact:

NIMH Lab of Brain and Cognition, NIMHLBCVolunteer@mail.nih.gov, 301-827-5157

<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

25-word description

Join an NIH Brain & Cognition Research Study enrolling ages 18-65, in good physical health. Help researchers learn more about how the brain works. Outpatient.

Contact:

NIMH Lab of Brain and Cognition, NIMHLBCVolunteer@mail.nih.gov, 301-827-5157

<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

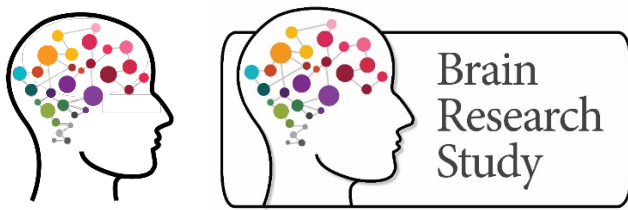
National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

HV Brochure, Print (listing in an NIH/NIMH Healthy studies brochure)

Brain & Cognition Research Study

This study seeks to learn more about how the brain works. Procedures may include: cognitive tasks, personality tests, brain imaging and/or magnetoencephalography (MEG) and electroencephalography (EEG). Ages 18-65. Protocol#: 93-M-0170

Twitter



<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

Join an NIH research study, help scientists learn more about how the brain works. Enrolling ages 18-65, in good physical health. [URL for study specific site will go here]

NIH Brain Research Study: Help scientists learn more about how the brain works. Enrolling ages 18-65, in good physical health. [URL for study specific site will go here]

NIH research study of how the brain works. Procedures may include cognitive tasks, personality tests, brain imaging. Ages 18-65. [URL for study specific site will go here]

Facebook



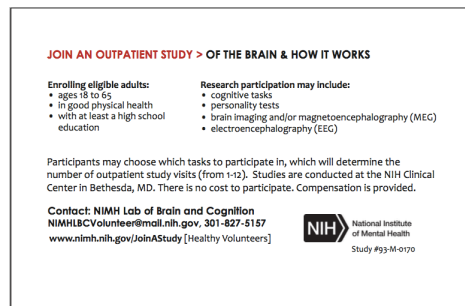
NIMH Brain & Cognition Research Study

Join a study seeking to learn more about how the brain works. Outpatient procedures may include: cognitive tasks, personality tests, brain imaging and/or magnetoencephalography (MEG) and electroencephalography (EEG). Ages 18-65. Protocol#: 93-M-0170. [URL for study specific site will go here]

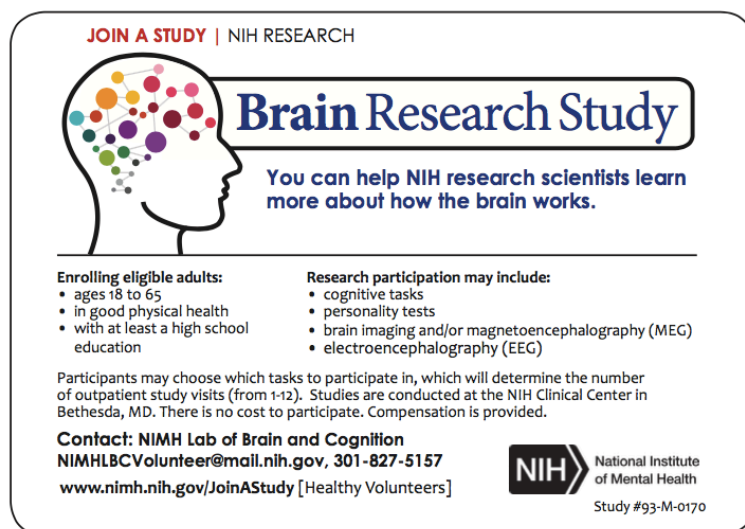
<https://www.nimh.nih.gov/labs-at-nimh/join-a-study/trials/adult-studies/brain-and-cognition-research-study.shtml>

Short URL: <https://go.usa.gov/xnCht>

Note Card



Card



Flyer

JOIN A STUDY > NIH RESEARCH

You can help research scientists learn more about how the brain works.



Brain Research Study

Enrolling eligible adults:

- ages 18 to 65
- in good physical health
- with at least a high school education

Research participation may include:

- cognitive tasks
- personality tests
- brain imaging and/or magnetoencephalography (MEG)
- electroencephalography (EEG)

Participants may choose which tasks to participate in, which will determine the number of outpatient study visits (from 1-12). Studies are conducted at the NIH Clinical Center in Bethesda, MD. There is no cost to participate. Compensation is provided.

Contact: NIMH Lab of Brain and Cognition
NIMHBCVolunteer@mail.nih.gov, 301-827-5157
www.nimh.nih.gov/JoinAStudy [Healthy Volunteers]



NIH Research Study:
Brain Imaging, Memory & Thinking
NIMHBCVolunteer@mail.nih.gov
301-827-5157
www.nimh.nih.gov/JoinAStudy

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www.nimh.nih.gov/JoinAStudy

NIH Research Study:
Brain Imaging, Memory & Thinking
NIMHBCVolunteer@mail.nih.gov
301-827-5157
www.nimh.nih.gov/JoinAStudy

Social Media (Pictures shown below will be used interchangeably)

Hashtags: #brain, #ClinicalTrial

Organizations and associations tags: @NIMH, NIMH Facebook page



Clinical Center Facebook

1. Healthy adult volunteers needed at the NIH Clinical Center for a research study. Researchers in the National Institute of Mental Health are using functional MRI, MEG and EEG to measure brain activity. Compensation provided. Call the Office of Patient Recruitment for more info: 1-800-411-1222. <https://go.usa.gov/x5t5b>
2. Healthy adults needed for a brain neuroimaging study at the NIH Clinical Center. Researchers are using functional MRI, MEG and EEG to measure brain activity.

Compensation provided. Call the Office of Patient Recruitment to participate: 1-800-411-1222. <https://go.usa.gov/x5t5b>

3. Researchers at the National Institute of Mental Health are seeking HEALTHY ADULT VOLUNTEERS for a neuroimaging study at the NIH Clinical Center measuring brain activity using functional MRI, MEG and EEG while participants are performing tasks. Compensation provided. <https://go.usa.gov/x5t5b>
4. NIMH researchers are using functional MRI, MEG and EEG to measure brain activity during tasks associated with perception, recognition, attention, and memory in a study at the NIH Clinical Center. HEALTHY ADULT VOLUNTEERS are needed. Compensation provided. <https://go.usa.gov/x5t5b>

Clinical Center Twitter

Healthy adults needed for brain imaging research study @NIHClinicalCntr using fMRI, MEG and EEG. <https://go.usa.gov/x5t5b>

OPR LISTSERV (“Current Protocols.” List of those interested in receiving updated protocol information via email. Links to this study on OPR recruitment website) and NIH LISTSERVs.

Healthy adults are needed for brain activity research study at the National Institutes of Health (NIH) in Bethesda, Maryland.

Researchers are using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) to measure brain activity as participants engage in tasks associated with perception, recognition, attention, and memory.

You may be eligible if you:

- Are 18-65 years old
- Have at least a high school education
- Are in good physical health

You may NOT be eligible if you:

- Have a past or present major medical, neurological, or psychiatric illness
- Had a serious head injury
- Have a learning disability
- Have a history of drug or alcohol abuse or dependence in the past 3 months (except nicotine)
- Are taking medications or supplements that may affect brain function
- Have serious vision or hearing problems
- Are unable to undergo an MRI (are pregnant, have metal in your body, cannot lie comfortably flat on your back for up to 3 hours)

Compensation is provided for study participation.

Location: The NIH Clinical Center, America’s research hospital is located on the Metro red line (Medical Center stop) in Bethesda, Maryland.

To participate, call:
Office of Patient Recruitment
1-866-444-1132
TTY: 1-866-411-1010
Online: <https://go.usa.gov/x5t5b>
NIH study 93-M-0170

Craigslist

Heading: NIH Research: Healthy adults needed for brain imaging study (NIH, Bethesda, Maryland)

Healthy adults are needed for brain activity research study at the National Institutes of Health (NIH) in Bethesda, Maryland.

Researchers are using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) to measure brain activity as participants engage in tasks associated with perception, recognition, attention, and memory.

You may be eligible if you:

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Compensation is provided for study participation.

Location: The NIH Clinical Center, America's research hospital is located on the Metro red line (Medical Center stop) in Bethesda, Maryland.

To participate, call:
Office of Patient Recruitment
1-866-444-1132
TTY: 1-866-411-1010
Online: <https://go.usa.gov/x5t5b>

NIH study 93-M-0170

ResearchMatch (Contact information and web links are not allowed)

Healthy adults are needed for brain activity research study at the National Institutes of Health (NIH) in Bethesda, Maryland.

Researchers are using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) to measure brain activity as participants engage in tasks associated with perception, recognition, attention, and memory.

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- Are taking medications or supplements that may affect brain function
- Have serious vision or hearing problems
- Are unable to undergo an MRI (are pregnant, have metal in your body, cannot lie comfortably flat on your back for up to 3 hours)

Compensation is provided for study participation.

Location: The NIH Clinical Center, America's research hospital is located on the Metro red line (Medical Center stop) in Bethesda, Maryland.

CC News/NIH Record

NIMH researchers seek healthy adult volunteers for a study using fMRI, MEG and EEG to measure activity in the brain during tasks associated with perception, recognition, attention, and memory. Participants will receive compensation. To participate, call: Office of Patient Recruitment 1-866-444-2214 (TTY 1-866-411-1010). Read about the study at <https://go.usa.gov/x5t5b>. Refer to NIH study #93-M-0170.

2. Recruitment text and banner for the sub-study “Using naturalistic and dynamic memory stimuli to investigate how the brain represents episodic memories over time”

Recruitment will be mainly conducted through the “1 Second Everyday App” using an IRB approved banner ad. However, any of the strategies listed in the recruitment section of this sub-study on page 82 and the Recruitment section on page 50 may be used.

NIMH-IRP Website: Join A Study

Category: Adult / Healthy Volunteers

Title: Memories and How the Brain Works

Enrollment: Local

Researchers are enrolling healthy volunteers for an outpatient research study to learn about the brain. A part of the study evaluates how the brain activates and represents memories. Participants will watch videos created in the “*1 Second Everyday App*” during a brain scan (MRI) and again during a MEG (magnetoencephalography) scan.

The study is currently enrolling eligible participants, between the ages of 18 and 65, who are in good physical health, and have at least a high school education. The study takes 4 hours and procedures include a physical exam, brain and MEG scans, and behavioral tasks.

The is conducted at the NIH Clinical Center in Bethesda, Maryland. There is no cost to participate and compensation is provided. For more information, contact: 301-827-5157, NIMHLBCVolunteer@mail.nih.gov.

TTY: 1-866-411-1010

URL: [URL for study specific site will go here]

Protocol #: 93-M-0170

Principal Investigator: Alex Martin, Ph.D.

Listserv (or Research Match, or craigslist)

Disclaimer: You are receiving this message because your email address is included in the above [insert listserv or mailing list]. The purpose of this message is to inform you of NIMH studies that are recruiting subjects. The moderator of the listserv/ mailing list has permitted its use for this distribution.

Memories and How the Brain Works

Join an NIH research study on the brain and how it works. A part of the study will evaluate how the brain activates and represents memories. Participants will watch videos created in the “*1 Second Everyday App*” during a brain scan (MRI) and again during a MEG (magnetoencephalography) scan.

The study is currently enrolling eligible healthy participants, between the ages of 18 and 65, who are in good physical health, and have at least a high school education, and live in the local Washington, D.C. metro region. The outpatient study takes 4 hours and procedures include a physical exam, brain and MEG scans, and behavioral tasks.

The is conducted at the NIH Clinical Center in Bethesda, Maryland. There is no cost to participate and compensation is provided. For more information, contact: 301-827-5157, NIMHLBCVolunteer@mail.nih.gov.

URL: [URL for study specific site will go here]

National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

Short Text

NIH Research Study: Memories and How the Brain Works

Join an outpatient research study enrolling healthy volunteers to help scientists learn more about the brain. Participation includes a physical exam, behavioral tasks, and watching videos created in the “*1 Second Everyday App*” during a brain scan (MRI) and again during a MEG (magnetoencephalography) scan. This part of the study is currently enrolling eligible adults ages 18 to 65, in good physical health, who have at least a high school education. There is no cost to participate and compensation is provided. The study is conducted at the NIH Clinical Center in Bethesda, MD.

Contact: 301-827-5157, NIMHLBCVolunteer@mail.nih.gov.

URL: [URL for study specific site will go here]

National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

25-word

Join an NIH Research Study: Memories and how the brain works while watching videos. Currently enrolling healthy participants ages 18-65 for a 4-hour outpatient visit.

Contact: 301-827-5157, NIMHLBCVolunteer@mail.nih.gov.

URL: [URL for study specific site will go here]

National Institutes of Health, National Institute of Mental Health, Protocol #: 93-M-0170

HV Brochure, Print

(listing in an NIH/NIMH Healthy studies brochure)

Memories & the Brain Research Study

This study seeks to learn more about how the brain works. Procedures in the memories part of the study include a physical exam, behavioral tasks, and a brain scan (MRI) and magnetoencephalography (MEG) while watching videos. Currently enrolling ages 18-65.

Protocol#: 93-M-0170

Twitter:

Join an NIH research study currently focusing on memories and how the brain works. Enrolling ages 18-65, 4-hour visit. [URL for study specific site will go here]

Memories & Brain Research Study at NIH: Enrolling ages 18-65. 4-hour visit, physical, behavioral tasks, brain scans while watching videos. [URL for study specific site will go here]

Facebook:

Memories and How the Brain Works

Join an NIH a research study currently enrolling healthy adults, ages 18-65, for 4-hours of procedures that include a physical exam, behavioral tasks, and brain scans while watching videos. Protocol#: 93-M-0170. [URL for study specific site will go here]

Flyer

NIH RESEARCH STUDY

How does the brain work while watching memories of your life?

A part of this study evaluates participants brain activity as they watch videos created in the "1 Second Everyday App."

The outpatient study takes 4 hours and is conducted at the NIH Clinical Center in Bethesda, Maryland. There is no cost to participate and compensation is provided.

Join a Study, Help us find out!

Currently enrolling eligible adults:

- ages 18 to 65
- in good physical health
- having at least a high school education
- living in the Washington, D.C. metropolitan area

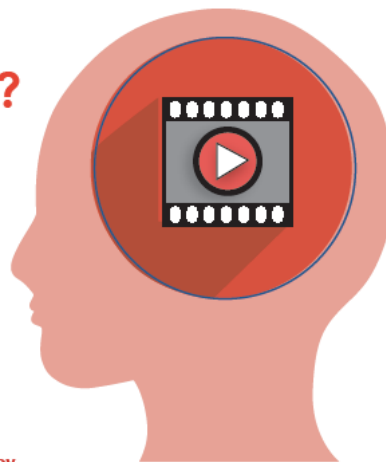
Research participation includes:

- a physical exam
- behavioral tasks
- a brain scan (MRI)
- magnetoencephalography (MEG)



Contact: 301-827-5157, NIMHLCVVolunteer@mail.nih.gov

www.nimh.nih.gov/JoinAStudy [Healthy Volunteers]

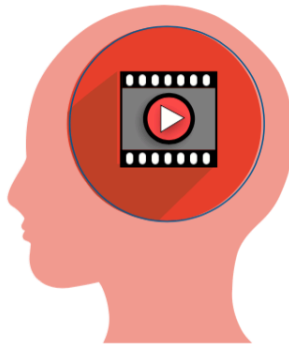


NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy	NIH Research Study: Memories & How the Brain Works NIMHLCVVolunteer@mail.nih.gov 301-827-5157 www.nimh.nih.gov/JoinAStudy
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One Second Video app banner:

Either of the following may be used.

**How does
the brain work
while watching
a movie of
your life?**



**Join a Study
Help us find out!**



Want to Join a Study?

**How does the brain work
while watching a movie
of your life?**

Help us find out!

CHECK IT OUT

D. Acknowledgement of Participation

Protocol Number: 93-M-0170

Title: Regional Cerebral Blood Flow studies of object perception, identification, localization, and memory

Date of Visit: _____

Associate Investigator: _____ **Research Assistant:** _____

I acknowledge that I have previously given consent to participate in the above protocol. Today I am participating in the following procedures (check all that apply):

- ☐ Neuropsychological Testing
- ☐ Behavioral Experiment
- ☐ MEG
- ☐ EEG
- ☐ MRI
 - ☐ 3T ☐ 7T
- ☐ Eye-tracking
- ☐ Physiological monitoring

Signature of Participant

Signature of Witness

Name of Participant

Name of Witness

Date

Date

MRN of Participant

E. Consent forms

Healthy adult volunteer

Consent for memory experiment

Consent for retrospective data sharing

F. Figures relating to sub-study “Using naturalistic and dynamic memory stimuli to investigate how the brain represents episodic memories over time”

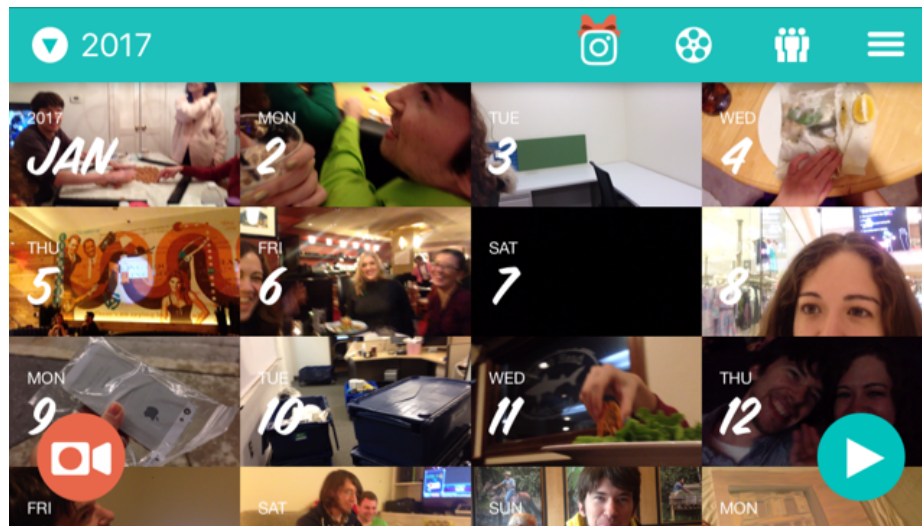


Figure 1 – A screenshot of the 1 Second Everyday interface. It is a calendar of a collection of the one second long videos chosen for each day. The “play” button creates a compilation of all of the videos in sequence. The second long videos as well as the final compilation are stored on the user’s phone and are never accessed by the app developers.

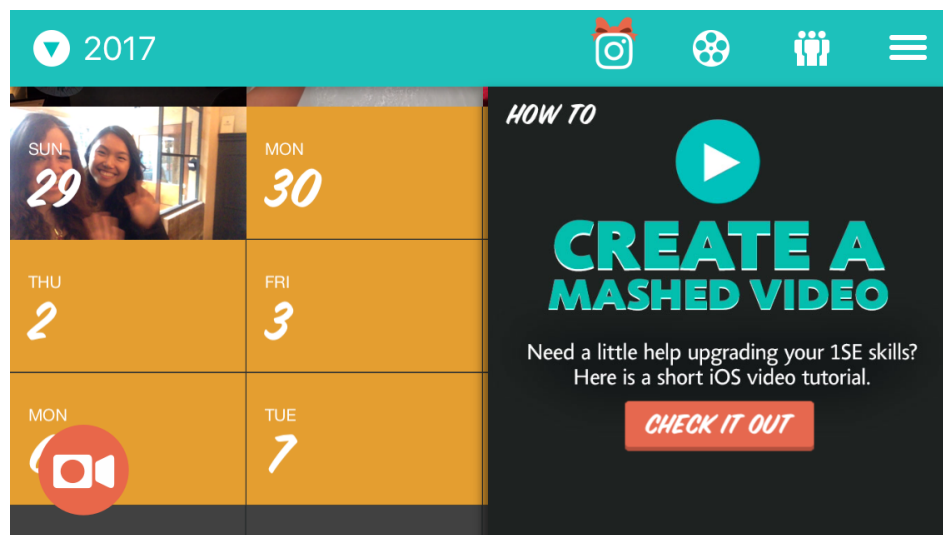


Figure 2 – The opening screen for the 1 Second Everyday app. On the right is a “banner” that shows news or tips for the app. A similar banner would be used to recruit participants for the study (see Appendix 25C-2 for the recruitment banner). The banner does not collect information on who viewed the banner, nor on who clicks it.

G. Sample Letter for Informed Written Consent for Retrospective Data Sharing via E-mail/Mail/FAX and Telephone Contact



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Building 10/Room 4C104
Bethesda, Maryland 20892-1264
Phone: 301-435-4932
Protocol Number 10-M-0047

<<Date>>

Dear <<Mr or Ms. Name>>,

We are contacting you because you previously participated in our study on <<ENTER DATE>> to learn more about the brain in healthy people (Studies of Blood Flow to the Brain During Thought, Protocol 93-M-0170). The purpose of this letter is to get permission to share your data with other scientists. Included with this letter are two copies of the informed consent. Soon you will be contacted by phone to assess your interest. If interested, a time will be arranged when a witness can be present on your end, to go over the consent and answer questions. We will then ask you to sign and date the consent form and have someone you know sign the consent form as a witness and send the consent form back to the investigator via FAX, e-mail or mail in the pre-paid envelope. The investigator who participated in the consent process will then sign the consent, and a copy of the consent with all three signatures will be sent to you.

You are under no obligation to share your data.

If you have any questions, please contact <<name of investigator>> at <<phone number of investigator>>.

Thank you for your time,
Alex Martin, Ph.D
Principal Investigator, Lab of Brain and Cognition
NIMH/NIH
301 435 4926

H. Authorization for recording, filming and photographing

Protocol Number: 93-M-0170

Title: Regional Cerebral Blood Flow studies of object perception, identification, localization, and memory

Date of Visit: _____

Investigator: _____ **Research Assistant:** _____

I, _____ authorize recording, filming or photographs, for the following purposes:

- The videos or photographs may be shown to other participants in the lab or on a testing website as part of online data collection for research purposes for this or other studies and protocols.
- The videos or photographs may be submitted to local, national and international data banks and shared with other qualified researchers globally.

Signature of Participant

Signature of Witness

Name of Participant

Name of Witness

Date

Date

I. Authorization for helmet construction

Protocol Number: 93-M-0170

Title: Regional Cerebral Blood Flow studies of object perception, identification, localization, and memory

Date of Visit: _____

Investigator: _____ **Research Assistant:** _____

I, _____ authorize recording, filming or photographs,
for the following purposes:

- The videos or photographs may be shared with a helmet manufacturer to produce an MRI/MEG compatible helmet based on my head shape.

Signature of Participant

Signature of Witness

Name of Participant

Name of Witness

Date

Date