Oscillatory Contributions to Working Memory and Attention

PI: Bradley R. Postle, PhD, Departments of Psychology and Psychiatry, University of Wisconsin–Madison

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Physiological and Behavioral Consequences of Brain Stimulation Renewal

Principal Investigator: Bradley R. Postle, Ph.D.

1. **Title**: Physiological and Behavioral Consequences of Brain Stimulation Renewal

2. **Summary of activities from protocol 2011-0608 and continuing studies for protocol 2016-0500:**

The approved sub-studies from the previous protocol, 2011-0608, fall into two categories, A or B. New sub-studies will be added to 2016-0500 in category B:

A. The sub-study is either complete, or in the final stages of data analysis. No further enrollment of subjects or research will be conducted on these sub-studies. The study documents such as signed consent forms and screening materials will be maintained for 7 years to address potential audits/NIH follow-up.

B. The sub-study is ongoing. A portion of the subjects have been enrolled or the sub-study has not yet begun. The research activities for the sub-study are currently ongoing.

A. The sub-study is complete or in the final stages of data analysis:
Sub-study A
Sub-study B
Sub-study C
Sub-study D
Sub-study E
Sub-study F
Sub-study G
Sub-study H
Sub-study I
Sub-study K
Sub-study L.1
Sub-study L.2
Sub-study N
Sub-study P
Sub-study Q
Sub-study R
Sub-study J
Sub-study S

B. The sub-study is ongoing:
Sub-study L.3
Sub-study M.1
Sub-study M.2
Sub-study T.1
Sub-study T.2
Sub-study O
Sub-study U
Sub-study V
Sub-study W
Sub-Study X
Sub-Study Y
Sub-Study Z
Sub-Study AA
Sub-Study AB
Sub-Study AC
Sub-Study AD
Sub-Study AE
Sub-Study AF

3. **Objectives of current sub-studies**:

The broad objective of the studies proposed under this protocol is to use transcranial brain stimulation, methods of non-invasive brain stimulation, to address questions about the functional anatomy of the human brain. Under this protocol These stimulation techniques offer advantages over measurement techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), in that they support inferences about causation, as opposed to correlation. The stimulation techniques covered by this protocol include transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). Previous work carried out by the PI's group under protocol 2011-0608 (which the present protocol is intended to replace) indicates that TMS interacts in interesting ways with cortical oscillations, and therefore offers a unique way to study the function of these physiological phenomena. The experiments described in this protocol fall into several methodological categories: simultaneous TMS and fMRI; repetitive or single-pulse TMS, which is administered alone, simultaneously with EEG, or before fMRI scanning; and tCS, which is administered via a cap that also affords simultaneous EEG recording. In all cases, these studies follow from work that has been carried out by the PI's group under protocol 2011-0608. In all cases, the experiments carried out under this protocol will test hypotheses about the neural bases of human perception, attention, and memory. Specific experiments differ from one another in terms of the details of the cognitive task(s) that subjects perform, but not in terms of the general TMS and/or physiological measurement (i.e., fMRI or EEG) procedures that are used. For this reason, this protocol will follow the

convention used in 2011-0608, in which each experiment is described as a "sub-study" of the protocol.

Simultaneous TMS and fMRI studies will begin with an MRI scan in order to acquire information about the subject's brain that is used for guiding the delivery of TMS (i.e., for "targeting"). On a different day, fMRI scanning is performed with a TMS coil that has been custom-designed to be compatible with the strong magnetic field generated by the MRI scanner. *Repetitive TMS or Single-pulse TMS* studies will also begin with an MRI or fMRI scan, followed, on a different day, by repetitive or single-pulse TMS that is delivered either alone. The EEG is recorded simultaneously, or before fMRI recordings. The initial scan is an MRI scan for experiments for which anatomical landmarks will be targeted by TMS. It is an fMRI scan of one or more areas of task-related activity are to be targeted with repetitive TMS. In such cases, subjects perform the cognitive task both during the initial fMRI scan and the subsequent repetitive TMS session. In some instances, high density EEG data (collected without concurrent TMS) can be recorded *simultaneously with fMRI* to obtain a higher temporal resolution, and to allow correlations between electrical activity and hemodynamic changes in the brain during tasks. EEG data can also be useful for pilot testing to refine EEG measurement and data processing procedures before a *simultaneous repetitive TMS and EEG* study is launched. Finally, *tCS* will be administered via a wireless hybrid EEG/tCS 8-channel neurostimulator system (model name "StarStim 8") manufactured by Neuroelectrics. The system's electrodes are held in a neoprene headcap that is worn by the subject. The cap is designed to allow for multiple configurations of tCS electrodes and EEG electrodes. This design affords the ability to record EEG signals prior to, during, and/or after stimulation.

3. **Rationale:**

In general, different substudies will utilize different approaches that rely on the various devices described in turn below. None of the substudies are intended to evaluate the safety/effectiveness of the devices. Rather, the devices are intended to be incorporated into this research as a tool to facilitate collection of data appropriate to address the over-arching research hypotheses. Any studies intended to evaluate device safety/effectiveness would be submitted under a separate protocol.

3.A. The inferential limits of neuroimaging

fMRI (as well as all other neurophysiological measurement methods, such as electrophysiology and positron emission tomography (PET)) is a correlative measure, and as such, data produced by fMRI alone are logically incapable of answering the question "does region X make a *necessary* contribution to function Y?" The only way to address conclusively questions about necessity is to alter the function of an area and to observe whether this perturbation has an effect on the function in question. The repetitive TMS experiment draws on this logic to ask questions of necessity that have arisen from previous neuroimaging studies.

3.B. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a technique introduced in 1985 (Barker, Jalinous, & al., 1985) that uses the principle of electromagnetic induction (the “right-hand rule” from high school physics) to get electrical energy across the scalp and skull in order to produce changes in neural activity in the brain. It involves placing a small coil of wire on the scalp and passing a very brief and powerful current through it. This produces a magnetic field that passes unimpeded through the tissues of the head. The magnetic field, in turn, induces a much weaker electrical current in the brain that is capable of activating nerve cells in the cerebral cortex. Thus, a TMS pulse produces a powerful but brief magnetic field that passes through the skin, soft tissue, and skull, and induces electrical current in neurons, causing depolarization that then may have behavioral effects. For example, if the hand area of primary motor area of the cortex is stimulated, twitches are easily recordable in hand muscles on the contralateral side of the body. TMS can be used to map the representation of body parts in the motor cortex on an individual basis, and is regularly used in neurology to determine central conduction times. (E.g., it is routinely used to track the progression of multiple sclerosis.) Subjectively, magnetic stimulation of motor cortex feels much like a tendon reflex movement (George, Lisanby, & al., 1999).

Applied as single pulses appropriately delivered in time and space, or applied in trains of repetitive stimuli at an appropriate frequency and intensity, TMS can be used to transiently alter the function of a given cortical target. In some applications it can have the effect of momentarily disrupting ongoing neural activity, thereby creating a temporary `virtual brain lesion' (Pascual-Leone, Walsh et al. 2000). This makes it possible to study two aspects of the contribution of a given cortical region to a specific behavior: `what does it do?' and `when does it do it?' For example, functional imaging studies of early or congenitally blind subjects reveal that their primary visual cortex can be activated by Braille reading and other tactile discrimination tasks. However, this activation could be an epiphenomenon of tactile information processing in blind people. Using TMS, it was shown that disrupting neural activity in primary visual cortex induced reading errors and distorted the tactile perceptions of congenitally or early blind subjects, thus demonstrating that the visual cortex is actually required for tactile spatial processing by early blind subjects (Cohen et al., 1997). There is a large body of work that has used TMS to induce ‘virtual lesions’ in order to establish the causal role of a cortical region in a given function, such as primary visual cortex in visual imagery, motor cortex in mental rotation, parietal cortex in attention, neglect and extinction, and frontal cortex in random number generation and working memory (Pascual-Leone et al., 2000; Walsh & Cowey, 2000). Indeed, the PI’s group has published several such studies under protocol H-2003-033 and 2011-0608 (Feredoes, Tononi et al. 2006; Postle, Ferrarelli et al. 2006; Feredoes, Tononi et al. 2007; Hamidi, Tononi et al. 2008; Hamidi, Tononi et al. 2009; Feredoes and Postle 2010).

Interestingly, TMS can be used not only to induce virtual brain lesions, but also to enhance functioning. There are two classes of examples of this. The

first is the treatment of psychiatric disorders. For example, as demonstrated by a number of studies, both high-frequency and low-frequency stimulation with TMS can have antidepressant properties (George et al., 1999). TMS has also been applied in schizophrenic subjects (Boroojerdi, Topper, & al., 1999; Cohen et al., 1999; Davey & Puri, 2000; Feinsod, Kreinin, Chistyakov, & Klein, 1998; Geller, Grisaru, Abarbanel, Lemberg, & Belmaker, 1997; Grisaru, Amir, Cohen, & Kaplan, 1998; Grisaru, Chudakov, Yaroslavsky, & Belmaker, 1998; Klein, Kolsky et al., 1999; Klein, Kreinin et al., 1999). For example, several studies have shown that TMS applied to temporal cortex of schizophrenic subjects can reduce the frequency and intensity of auditory hallucinations (Hoffman et al., 1999; Hoffman et al., 2000). These studies have triggered great interest in the potential therapeutic applications of TMS. The second class of “enhancing” effects has been pioneered by the PI’s group, with the discovery (via simultaneous TMS-EEG) that repetitive TMS can have differing results on task-related EEG for different subjects, with these effects predicting whether repetitive TMS will have performance-enhancing or performance-impairing effects for any given individual (Hamidi, Slagter et al. 2009; Johnson, Hamidi et al. 2010). More recently, repetitive TMS using a continuous theta burst stimulation paradigm (TBS, similar to sub-study G, which has been completed on the 2011-0608 protocol) has been shown to induce robust performance-impairing effects during working memory tasks that can last up to one hour (Morgan et al, 2013; Lee and D’Esposito 2013). It has also been demonstrated that several daily sessions of TBS can have positive clinical effects in pathological disorders such as auditory hallucination (Kindler et al, 2013) and amblyopia (Clavagnier et al, 2013). These results are exciting, in that they suggest that it may be possible to tailor the delivery of repetitive TMS to an individual such that it can be used either therapeutically or diagnostically.

However, the satisfactory development of such applications requires a better understanding of which brain circuits are activated or deactivated as a result of TMS of a given brain area (Pascual-Leone, Walsh et al. 2000). For example, investigators are only beginning to appreciate that whether repetitive TMS has disruptive or facilitative effects on cognitive task performance can depend on the frequency of repetitive TMS with respect to the subject’s IAF (Klimesch et al, 2003; Luber et al., 2007). In this context, recent work attempting to combine TMS with functional neuroimaging is particularly relevant.

3.C. Transcranial magnetic stimulation and functional neuroimaging

Paus *et al.* (Paus et al., 1997) were the first to introduce the combined techniques of TMS and functional neuroimaging as a means of mapping neural connections in the live human brain. They used TMS to stimulate directly a selected cortical area; simultaneously, they measured changes in brain activity, indexed by cerebral blood flow (CBF). Ilmoniemi *et al.* (Ilmoniemi, Virtanen et al. 1997) used a similar approach for studying cerebral connectivity in humans using a combination of TMS and quantitative EEG. In their first study, Paus *et al.* (Paus et al., 1997) applied TMS to the left frontal eye fields of human subjects and found a significant positive correlation between the number of TMS pulses

and CBF at the stimulation site and, most importantly, in the superior parietal and medial parieto-occipital regions. The pattern of these distal effects was consistent with the known anatomical connectivity of monkey frontal eye fields. The authors concluded that the combination of TMS with functional neuroimaging offers an objective tool for assessing the state of effective connectivity without requiring the subject to engage in any specific behavior (Paus, 1999). Mottaghy *et al.*(Mottaghy, Krause et al. 2000) have combined TMS and PET in humans to investigate the role of prefrontal cortex in working memory. They found that, while both left and right prefrontal TMS affect performance in a working memory task, right-sided TMS has stronger and longer effects. Interestingly, the PET study showed that left dorsolateral prefrontal cortex TMS produced reductions in cortical activity only in the directly targeted prefrontal region. By contrast, TMS to the right prefrontal cortex significantly reduced activity in the right prefrontal region, the right fronto-temporal pole, and bilateral parietal regions. This result indicates that, while the anatomical connectivity of left and right dorsolateral prefrontal cortex is similar, their effective connectivity may be quite different.

In the first combined simultaneous fMRI/TMS study in humans, Bohning et al. showed that 18-second trains of TMS pulses at 1 Hz (18 pulses at 110% of motor threshold (MT)) induced 3%-4% increases in the blood oxygenation level-dependent (BOLD)-fMRI signal in the area of stimulation (Bohning et al., 1999; Bohning et al., 1998). Although that study had an imaging time resolution of 3 seconds rather than the approximately 60 seconds in the PET studies, it used a block design stimulation pattern, so the hemodynamic response could not be directly compared with the hemodynamic response observed in cognitive task single-event studies. Bohning et al. also demonstrated BOLD-fMRI responses to single TMS pulses over human motor cortex in both the ipsilateral motor cortex under the TMS coil and the contralateral motor cortex (Bohning et al., 2000). The associated BOLD signal increase showed the typical fMRI hemodynamic response time course. More recently, using TBS on the prefrontal cortex before a working memory task performed in the MRI scanner, Lee and D'Esposito showed a decreased of the tuning of extrastriate cortex responses, coinciding with decrements in performance. They also found that activity in the homologous prefrontal region in the non-stimulated hemisphere predicted performance following disruption (Lee and D'Esposito, 2012). Similarly, TBS on the prefrontal or parietal cortices has been shown to selectively impair working memory for visual-spatial conjunctions (Morgan et al, 2013). The combination of TMS and fMRI technique is important because it allows the comparison of different TMS events using their associated BOLD responses. These studies demonstrate the feasibility of combined fMRI/TMS paradigms in humans to probe activity in different brain regions in a systematic manner.

3.D. Combining TMS and EEG

In TMS, the cerebral cortex is stimulated non-invasively by generating a brief but strong magnetic pulse (<1 ms, up to 2 Tesla) through a coil applied to the surface of the scalp. The rapid change in magnetic field strength induces a

current flow in the tissue, which results in the activation of underlying neuronal populations (Hallet, 2000). The synchronous volley of action potentials thus initiated propagates along the available connection pathways and can produce an evoked response in target cortical regions. Typically, if the primary motor area of the cortex is stimulated, twitches are recordable in muscles on the other side of the body. Most of the electrophysiological studies on TMS-evoked responses have been limited to the measurement of the motor output. Until recently, the effects of TMS on cortices other than motor cortex have been limited solely to the registration of the behavioral effects of the stimulation. The first studies of cortico-cortical responsiveness have used TMS and positron emission tomography (PET) in conjunction (Paus et al., 1997; Paus, 1999). This approach offers a good spatial resolution but suffers from a very low temporal resolution with respect to the actual dynamics of the response.

The combination of TMS and EEG represents a unique tool for investigating the effects of repetitive TMS on endogenous oscillations in neuronal populations, a factor that may determine whether the effects of repetitive TMS on behavior are facilitatory or disruptive in any particular situation. The simultaneous use of TMS and EEG, however, is challenging and has required the solution of several technical problems. A major one is the EEG artifact induced by the magnetic pulse. During stimulation, the strong magnetic field generated by the coil can induce voltages between scalp electrodes that can reach several volts, i.e. six orders of magnitude larger than the typical EEG signal. The volt-level peak in the leads saturates the input stages of the standard EEG amplifier, requiring several seconds for the circuits to return in the linear operating range. To overcome this problem, Virtanen and collaborators have designed and built a 60-channel EEG acquisition system that prevents large artifacts thanks to gain-control and sample-and-hold circuits that pin the amplifier output to a constant level during the pulse (Virtanen et al., 1999). In a first study combining TMS/EEG, the motor cortex of normal volunteers was activated by single TMS pulses while recording electrical brain activity with 20 scalp electrodes (Ilmoniemi, et al., 1997). After the pulse, an immediate response over the left sensory-motor area was followed by the spread of activation to adjacent ipsilateral motor areas within 5-10 ms and to homologous regions of the opposite hemisphere within 20 ms. In a more recent study by the same group (Komssi et al., 2002), TMS-evoked scalp potentials were recorded with a high-density array (60 leads) and superimposed on magnetic resonance images. The results confirmed specific ipsi- and contralateral EEG responses that varied depending on the precise site of stimulation in the left sensory-motor cortex. Using a similar technique, Paus et al. (2001) demonstrated that TMS in the human primary motor cortex induces both local synchronization and evoked waves at distant locations. Interestingly these responses were often detectable in single EEG traces. Altogether, these results indicate that the effects of TMS on endogenous oscillatory activity can now be studied in the human brain with high spatial resolution and on a millisecond time scale by combining TMS and EEG. As described in his HS-IRB protocol # 2003-238, Dr. Giulio Tononi's group acquired the first commercially available version of the system used by Komssi

et al. (2002), which is manufactured and sold by Nexstim, Ltd. Dr. Postle's group has now acquired an identical system, which is located at the HealthEmotions Research Institute (HERI), and the proposed repetitive TMS-EEG experiments will be performed with this system.

3.E. Combining EEG and fMRI

Simultaneous EEG-fMRI recordings offer the possibility of enriching the significance and the interpretation of results from single modality experiments because they provide simultaneous, complementary measures of the same neural processes underway in the same brain. The combination of EEG with fMRI has been successfully used by other investigators to observe changes in brain activity during working memory tasks (Scheeringa et al 2009, Michels et al 2010, 2012, Chaudhary et al 2012, White et al 2012). For instance, Sheeringa et al (2009) identified the emergence of functional (MRI) networks related to alpha and theta EEG power increases during working memory maintenance, and showed that theta power during encoding predicted subsequent-memory performance and default mode network deactivation (White et al 2012). The coupling of frequency band oscillation and the BOLD signal in task-related areas permits the observation of changes with cognitive load, e.g., theta band power increased with load in frontal midline regions (Michels et al 2010). These studies demonstrate the feasibility of combined EEG-fMRI paradigms which provide complementary information: fMRI can show changes in blood flow and activity in deeper brain structures while EEG, which is limited to electrical activity at the brain surface, has the best temporal resolution and can measure changes in activity much more quickly than fMRI. Note that the EEG system (Brain Products GmBH, Germany) is compatible with the MRI equipment, and has been approved for use in the identical MRI conditions by the HS-IRB in previous protocols from Dr. Giulio Tononi's group (H-2004-0023, H-2007-0150, H-2013-0019), and the PI's previous protocol, 2011-0608.

3.F. tCS

3.F.1. General description of method

Transcranial current stimulation (tCS) is a non-invasive painless method to affect cortical excitability by using weak electrical currents (typically in the range of 1-to-2 mA) applied to the scalp of the subject. tCS can be administered in three modes: direct-current stimulation (tDCS); alternating-current stimulation (tACS); and random-noise stimulation (tRNS). The literature contains reports of thousands of tCS sessions that, when following standard procedures, have been carried out without any injury to skin or underlying tissue (Woods, Antal et al. 2016). We will begin with tDCS, because its principles and application are easiest to explain.

3.F.2. Using *tDCS* involves passing current through the skin, skull, and brain with a direct-current device. By analogy, a battery is a device that we all

have experience with that delivers direct current. If one connects a fresh 9-volt battery to an oscilloscope, one will see the scope jump from 0 volts to 9 volts as soon as the battery terminals (the positive (i.e., the cathode) and the negative (i.e., the anode)) are attached to the two probes. When one of these probes is taken off, the circuit is "broken", and the measured voltage returns to 0 volts. The method of tDCS entails passing precisely this same kind of constant current (albeit at markedly lower intensity) through a circuit, with the tissue of the brain serving as a part of the circuit, typically for a fairly long period of time (e.g., 20 min). Importantly, the electrical currents from tDCS (typically 1-2mA on the scalp) are far too low to directly induce action potentials in cortical neurons. Instead, their effects are on cortical excitability via changing the transmembrane potential of neurons (Iyer et al., 2005; Nitsche & Paulus, 2000; Wagner et al., 2007). This has the functional effect of modulating the processing carried out by the stimulated area. For example, Nitsche and Paulus (2000) showed that exciteability of primary motor cortex can be modulated by up to 40% with tDCS as measured by the size of motor evoked potentials induced with transcranial magnetic stimulation (TMS). That is, tDCS all by itself didn't generate motor evoked potentials, but the amplitude of potentials evoked by a pulse of TMS was higher when TMS was delivered concurrently with tDCS. Similar results have been found for changes to TMS-evoked phosphenes when applying tDCS to primary visual cortex (Antal, Kincses, Nitsche, & Paulus, 2003). Importantly, the direction of the effect of tDCS – that is, excitation or suppression of exciteability -- depends on the polarity of the stimulation. Cortical excitability tends to be reduced in brain tissue nearest the cathode, whereas it is increased in tissue nearest the anode. In typical applications of tDCS, only the anode or the cathode of the stimulator is placed over cortex, with the other terminal placed on a part of the body away from the brain. Thus, a tDCS stimulation protocol is referred to as being "anodal" or "cathodal".

3.F.3. *tACS* also involves passing current through the skin, skull, and brain with an electrical stimulator. The difference from tDCS, as conveyed in the name, is that tACS entails the delivery of alternating current (rather than the direct current of tDCS). That is, with tACS the current fluctuates sinusoidally, such that during one half of each cycle one electrode serves as anode and the other one as cathode, and for the other half of the cycle the pattern reverses. Thus, during tACS, the *average* membrane potential does not deviate from its baseline level. Unlike tDCS for which the experimental goal is to tACS is put a region of the brain into a prolonged, steady state of increased or decreased exciteability, tACS is typically used to influence neuronal oscillations (Herrmann et al., 2013).

3.F.4. *tRNS* is a variant of tDCS, but for which the DC current is held at any given level for a relatively brief period of time (typically, on the order of seconds), and is randomly stepped between different levels. The mechanisms by which tRNS can influence behavior are poorly understood, although the principle of stochastic resonance has been proposed. Because we are not

proposing to use tCS in tRNS mode, tRNS will not be considered further in this protocol.

4. Potential Adverse Events:

Please note that each of the entries on this list is "hypothetical", in the sense that the nature of these procedures is such that it is reasonable to be concerned that such potential adverse events might be a possibility, and in many cases there is a literature exploring such potential events. In the experience of our laboratory, however, which extends back to 2007 with EEG (2003-033), to 2003 with TMS (2003-033 and 2011-0608), and to 2000 with fMRI (2005-503 and 2012-0652)), no instance of any of these potential adverse events has occurred.

4.A. TMS

4.A.1. Seizure Induction

The major safety concern about TMS is the possibility of eliciting a seizure, although TMS has rarely been associated with the induction of seizure, even in patients with epilepsy. TMS regimes are subdivided into single-pulse, low frequency (<= 1Hz), and high frequency (> 1Hz). Seizure induction, although exceedingly rare, is almost exclusively observed after high-frequency TMS well above 1Hz *and* with long stimulation trains (Hallett, Wassermann, Pascual-Leone, & Valls-Sole, 1999; Wassermann, 1998). A few reports have suggested TMS-related seizures occurred after single pulses, but all of these were in subjects with epilepsy or other neurological conditions (Classen et al., 1995). No seizures have been reported in normal volunteers receiving single pulse TMS, nor in patients diagnosed with depression or schizophrenia. Seizures have never been reported in subjects receiving 1 Hz TMS. For high frequency studies (i.e., repetitive TMS), precise stimulation guidelines have been published that specify conservative safe stimulation regimes (Wassermann 1998). More recently, these were reaffirmed by the Safety of TMS Consensus Group (Rossi, Hallett et al. 2009). In the simultaneous fMRI/TMS study, we will exclusively employ single-pulse or low-frequency stimulation regimes (less than or equal to a single pulse/sec), which are safe with respect to seizure induction. In the repetitive TMS study, the combination of stimulation parameters (i.e., intensity, rate, and duration) will fall within the established safety parameters established at the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (Chen and al. 1997; Wassermann 1998). For repetitive TMS using TBS, the risk of seizure is comparable to or less than the other conventional high frequency repetitive TMS protocols (Rossi et al 2009, Oberman et al, 2011). The bulk of the existing literature on the safety of magnetic brain stimulation has focused on single pulse TMS, and no adverse effects have been reported in the numerous studies in normal and clinical populations. It is considered safe with magnetic fields up to 2T, charge density of less than 40 $\mu C/cm^2$ per phase, and at repetition rates less than 3 per second (Agnew & McCreery, 1987; Gordon et al., 1990). The Magstim magnetic stimulator used in

this protocol has a maximal magnetic field strength of 2T (which diminishes to 0.2 mT 1 meter away from the coil), and the maximum repetition rate is 8 per second at full power (30 per second maximum). In reference to single pulse stimulation, the FDA has reported that “this type of transcranial magnetic stimulator does not now present a potential risk to health, safety, or welfare of subjects” (Glass, 1995). Prospective studies designed to systematically evaluate health effects have not found changes in EEG, blood pressure, pulse, serum cortisol, serum prolactin, cerebral blood flow, memory or cognition (Hamano, Kaji, Fukuyama, Sadato, & Kimura, 1993; Levy, Amassian, Schmid, & Jungreis, 1991; Wassermann et al., 1996), (see Wassermann 1998 for review). Single pulse TMS of the motor cortex has been used safely in normal children and infants as young as 2 weeks of age (Muller, Homberg, Coppenrath, & Lenard, 1991; Rossini & Caramia, 1992). Single pulse TMS is now in routine clinical diagnostic use in hundreds of neurophysiological laboratories world-wide.

As the potential for the use of TMS has grown, repetitive TMS is being utilized in neuropsychological experiments more often. The major risk that is associated with repetitive TMS is seizures. Repetitive TMS has been known to elicit seizures in a small number of subjects since its introduction in 1989. In all cases, the seizures showed immediate slowing after the TMS was shut off and was normalized within 1 to 2 days. However, each of these subjects was stimulated with a pulse of extremely high intensity or frequency, or with a very low intertrain interval. Subsequent studies have shown that if the stimulation intensity, frequency, duration, and total number of pulses delivered per day are within the established safety parameters, and there is no history of seizures in the subject or his or her family, then repetitive TMS can be safely utilized in scientific experiments (Anand and Hotson, 2002; Wasserman, 1998; Rossi et al., 2009, Anderson, 2006). Previous studies producing momentary disruption of cognitive functions of the cerebral cortex with repetitive TMS have used stimulation parameters well within the safety parameters mentioned above (Pascual-Leone and Hallett, 1994; Mottaghy, et al. 2002). Testing of subjects following repetitive TMS stimulation has shown no neuropsychological deficits (Pascual-Leone, et al. 1993).

4.A.2. Headache and mood changes

The most commonly reported side effect of TMS is headache of muscular origin (<5%). Neck pain or scalp pain may also occur. Both typically last up to a few hours on the day of stimulation and are usually managed easily with standard analgesics (single doses of aspirin or acetaminophen). 1Hz TMS given to the prefrontal cortex has been reported to improve mood in patients with depression. Mood assessments will be conducted to detect if any mood effects are seen in this study. We will inform subjects about possible alterations in mood and ask them to report any change immediately.

4.A.3. Magnetic Effects

Human tissue is virtually nonreactive to magnetic fields (Cadwell, 1991). The peak field strength of the device used in this protocol is <2T and the peak

magnetic field achieved with the 70 mm figure eight or 90mm circular stimulating coil is <1.5T. These figures are within federal guidelines for whole body exposure to static magnetic fields during Magnetic Resonance Imaging ((Schaefer, Bourland et al. 2000); United States Food and Drug Administration, Magnetic Resonance Diagnostic Devices Criteria for Significant Risk Investigations, at URL http://www.fda.gov/cdrh/ode/magdev.html, 1997). According to the World Health Organization task group report, there are no adverse effects on human health from short-term exposure to static fields up to 2T. Exposure to the static field during an MRI is commonly on the order of two hours. For comparison, the maximal cumulative exposure time to magnetic fields in this protocol is less than 0.032 seconds for single pulse TMS and less than 0.048 seconds for repetitive TMS. Subjects with metallic or electronic implants will be excluded, due to the risk that magnetic field exposure may affect the functioning of such implants.

4.A.4. Effects of Induced Electrical Current

The maximal induced electrical current from individual TMS pulses is well below levels that would lead to neuropathic effects. The maximum induced electrical field and current density per phase are 410V/m and 14 mA/cm^2. These values are similar to those used with conventional transcranial and direct cortical electrical stimulation. The maximal charge density per phase is calculated to be ≈ 0.94 μC/cm2 (Jalinous, 1991). In animal studies, Agnew and McCreery (1987) found no signs of neuronal damage with a higher charge per phase of 10μC/cm^2 when using direct intracranial electrical stimulation at 50 Hz continuously for 24 hours. The threshold for neuronal injury was a charge density per phase of 40 μC/ cm^2.

Many histopathological studies in animals have failed to show pathological changes in brain after repeated magnetic stimulation (Sgro, Ghatak, Stanton, Emerson, & Blair, 1991). The safety of repeated pulses may be proportional to the degree to which they exceed motor threshold. Matsumiya (1992) found that repeated pulses only produced structural changes when their intensity exceeded 3.4 times the motor threshold. Neuronal injury occurring at these high intensities may well have been secondary to intense head jerking in the unrestrained rodents tested. Two epileptic patients have had histochemical evaluation of surgically removed temporal lobes following rapid-rate TMS up to 16 Hz, 10 sec trains, and up to 1260 total stimuli. No pathological changes attributable to TMS were found (Gates, Dhuna, & Pascual-Leone, 1992).

4.A.5. Sound Exposure

When producing a magnetic pulse train, the stimulating coil produces a series of brief clicks. Animal studies have demonstrated that ear plugs prevent changes in auditory thresholds despite extensive exposure to long term, repeated, high intensity stimulation with associated sound output of up to 157 dB peak sound-pressure levels (Counter, 1994). No evidence of hearing loss has been found in humans exposed to TMS, despite extensive exposure to repeated stimulations over several years (Pascual-Leone et al., 1992). Subjects

will either wear earplugs (if no EEG recording) or earphones through which a white noise will be played throughout each TMS session. This latter procedure has been successfully applied in previous studies in order to prevent contamination of TMS-evoked EEG potentials by the auditory response to the coil's 'click' (Massimini et al 2005, 2010, Rosanova et al 2012, Johnson et al 2012).

4.B. fMRI

The functional MRI experiments will be conducted using a 3.0 tesla scanner (GE Discovery MR750) at the Lane Neuroimaging Laboratory (HERI). This fMRI system is FDA approved, and its software incorporates the necessary limitations for meeting FDA regulations for safe scanning of patients. The principal investigator currently has HS-IRB approval to use these scanners under HS-IRB 2012-0652.

Patient screening for MRI contraindications: each subject will be required to fill out an MRI screening form that will determine whether the subject has any contraindications for MRI. If it is determined that a subject has a specific contraindication, such as metal or electronic implants, he/she will be excluded. (Note that this does not apply to subjects in "EEG-only" sessions that do not involve MRI or fMRI.)

Patient comfort. Study subjects will be monitored both visually and by intercom, so that if the need should arise, they will be moved promptly from the magnet. Fans, intercom, cushions, blankets, hearing protection and proper lighting are standard comforts for all patients inside the magnet.

4.C. EEG

Electroencephalography is a technique commonly used to measure non-invasively electric brain activity both in research and in the clinic. In this study we intend to employ an EEG amplifier specifically designed for TMS compatibility. The HS-IRB has previously determined, for the PI's protocol 2003-238, and more recently, 2011-0608, that this device can be categorized as "non-significant risk (NSR)". This device, produced by Nexstim Ltd. (Helsinki, Finland), is the first commercially available TMS-compatible EEG amplifier and conforms to applicable safety standards for medical devices IEC60601-1, IEC60601-1-4, IEC60601-2-26 (certificates by the regulatory body were provided for the approval of HS-IRB protocol 2003-238, and more recently, 2011-0608). The device is based on a standard electroencephalographer but features a proprietary circuitry that allows the rejection of the artifact caused by the TMS pulse, thus making possible continuous EEG acquisition during TMS. We will also use another EEG system that is compatible with MRI (Brain Products GmBH, BrainAmp MR Plus MRI compatible high density EEG system, Germany). See http://www.brainproducts.com/productdetails.php?id=6). Finally,

for some of the “EEG-only” studies (see section 8.C. below) included in the protocol, we will use an EEG system that will be housed in the PI’s laboratory at the Brogden Psychology building. Although this system is not intended to be used with TMS for this research protocol, the system is TMS-compatible (Brain Products (brainproducts.com) actiCHamp Plus 64-channel high density EEG System, USA).

Electroencephalographers are considered non-significant risk devices by FDA [21 CFR 812.2(b). An NSR device is defined as a device that does NOT present a potential for serious risk to the health, safety, or welfare of a subject and is NOT: (1.) an implant; (2.) used in supporting or sustaining human life; (3.) of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; (4.) otherwise a potential for serious risk to the health, safety, or welfare of a subjects. The devices have previously been found by the HS-IRB to meet criteria from 1 to 4 of the FDA information sheets, and the procedure to obtain the EEG is regularly carried out by researchers and clinicians throughout the world and there is no history of safety problems.

We foresee no risk from EEG recording. However, some individuals with very sensitive skin may experience, on rare occasion, a slight irritation at the site of sensor application due to the use of mildly saline conductive gel. Regarding the combination of EEG with fMRI, there are no foreseeable additional risks.

4.D. Positioning System

The EEG system from Nexstim Ltd. (Helsinki, Finland) also includes a frameless positioning device, namely, an optical tracking system that measures the 3D position of markers, and thereby determines the real-time position and orientation of the tool with markers. The frameless positioning unit helps to relate the location of a tool outside the subject's head with respect to the subject's structural magnetic resonance images. The product is designed to support and guide the positioning of non-invasive magnetic stimulation coil (not included) over predefined anatomical structures in scientific and clinical procedures. The optical tracking unit applies harmless infrared light to measure the location of the tools. The unit is manufactured by Northern Digital Inc, Canada, according to the applicable medical safety standards IEC60601-1 and UL2601-1.

Given that the positioning device is entirely passive, and not in touch electrically with the subject/patient, the device is harmless.

4.E. tCS

tCS is delivered via an electrodes encased in sponge (to prevent direct contact with the skin), with the sponge moistened with a conductive medium, typically saline or electrode gel. The tDCS parameters employed under this protocol will always be within the range used in published work with respect to variables that are relevant to safety: current density, current strength (up to 1.75

mA), duration (up to 20 minutes) of treatment, and total charge. We will not exceed a current of 1.75 mA; using this current and electrodes with a contact size of 5x7 cm, we will have a maximum current density at the skin of .05 mA/cm^2, a value well within safety guidelines proposed by Nitsche al. (2003). These currents are also well below those induced by transcranial magnetic stimulation, which is in the range 14 mA/cm^2, and is approved by several current HS protocols, including the PI's 2016-0500. McCreery et al. (1990) have shown that current densities below 25 mA/cm^2 do not induce brain tissue damage even by applying high-frequency stimulation over several hours. For comparison, the maximum current we propose to apply is 500 times lower than this. Additionally, given the brief duration of the stimulation (up to 20 minutes per session), the delivered amount of charge of .06 C/cm^2 which is 3600 times less than the minimum amount of charge associated with tissue damage (216 C/cm^2, Yuen et al., 1981).

Stimulation will be conducted by the principal investigator or a trained research assistant. Research assistants conducting the study will always undergo a formal training session in the use of the device by the principal investigator. The training session will include hands-on practice soaking the electrode pads in saline solution. The principal investigator will create documentation for each individual research assistant that will administer tDCS which specifies that they have completed this device training.

Experiments involving the administration of tDCS will have the same essential design; we will seek evidence of tDCS on behavioral tasks that have minimal risk. To this end, subjects will typically be tested during or after tDCS; effects of tDCS (either disruption or enhancement) will be sought by comparing performance between stimulation conditions and at different times (i.e. during vs. post-stimulation). The identical procedure will be used within a single study to allow for comparison between conditions, however the procedure may change between studies. For example, in a case of an task that lasts for longer than 15-20 minutes (the typical length of tDCS stimulation), the most powerful way to measure effects of stimulation is to assess performance during the initial part of the experiment that includes stimulation and compare it to performance in the latter part of the experiment (post-stimulation). By computing the interaction (i.e., slope difference) for performance during stimulation and post-stimulation as a function of stimulation condition (sham, cathodal, anodal), we can effectively measure the effect of different stimulation conditions.

The experiments will also include a sham stimulation condition. In this condition, a 1-1.75 mA current will be delivered for approximately 10 seconds at the beginning of the sham condition before being extinguished over the course of 5 seconds. This brief current may cause a slight tingling or itching sensation at the initiation of treatment. With this brief current at the initiation of the sham treatment, many investigators have found that subjects could not distinguish between real and sham treatment (Gandiga et al, 2006).

5. **Study Design**:

All studies will be performed at HERI, which houses both the Lane Family Neuroimaging Laboratory (a 3T MRI scanner) and the electrophysiology laboratories of Dr. Tononi and Dr Postle which house the EEG and TMS equipment. Note that only people listed as Key Personnel for this study are involved in any of the research procedures, and only those listed as Key Personnel have access to the study data and are involved in the analysis of study data. They will enroll young adults (between the ages of 18-35) free from any neurological or psychiatric diagnosis.

6. **Study Duration**:

Below, the study duration is denoted for each sub-study:

A. Sub-study L.3 (TMS/EEG_1D): One 1 hr MRI visit for localization. Two-three 4-hr TMS/EEG sessions.
B. Sub-study M.1 (TMS/EEG_motion): One 1 hr MRI visit for localization. Two 4 hr TMS/EEG sessions.
C. Sub-study M.2 (TMS/EEG_motion_color): 1 hr MRI visit for localization. Two 4 hr TMS/EEG sessions.
D. Sub-study T.1 (UMI1): three sessions (a training session in fMRI scanner, TMS/fMRI session targeting IPS, TMS/fMRI session targeting LASSO-identified cortex, each up to 2 hr in length.
E. Sub-study T.2 (UMI2): three sessions (a training session in fMRI scanner, TMS/fMRI session targeting IPS, TMS/fMRI session targeting LASSO-identified cortex, each up to 2 hr in length.
F. Sub-study U (EEG Training): One visit 3.75 hr for EEG session, 5 hours per week for 2 weeks of training on the material, and a subsequent 3.75 hr visit for a final EEG session.
G. Sub-study O (Biacom EEG): One 2 hr visit for EEG session.
H. Sub-study V (FREQMOD): One 1.5-hr visit for EEG session
I. Sub-study W: One 1.5-hr visit for tCS session
J. Sub-study X: One 2.5-hr visit for tACS session
K. Sub-study Y (2Back EEG): One 2-hr visit for EEG session
L. Sub-study Z: (SPACEORDEREEG): One 3-4-hr visit for EEG session
M. Sub-study AA: (SPACETIME EEG): One 3-4-hr visit for EEG session
N. Sub-study AB: (LTM EEG): One 1-hr for behavioral session; Two 3-4 hr visits for EEG sessions
O. Sub-study AC: (DACOM): One 3-4-hr visit for EEG session
P. Sub-study AD: (MFE): One 3-4 hr visit for EEG session
Q. Sub-study AE: (HAMS): One 4 hour visit for EEG session
R. Sub-study AF: (PIII): One 4-hour visit for EEG session

7. **Subject Population**:

Below, the subject population is denoted for each sub-study:

A. Sub-study L.3 (TMS/EEG_1D): 24 subjects

B. Sub-study M.1 (TMS/EEG_motion): 24 subjects

C. Sub-study M.2 (TMS/EEG_motion_color): 24 subjects

D. Sub-study T.1 (UMI1): 24 subjects

E. Sub-study T.2 (UMI2): 24 subjects

F. Sub-study U (EEG Training): 24 subjects

G. Sub-study O (Biacom EEG): 24 subjects

H. Sub-study V (FREQMOD): 24 subjects

I. Sub-study W: 24 subjects

J. Sub-study X: 24 subjects

K. Sub-study Y: 42 subjects

L. Sub-study Z: 24 subjects

M. Sub-study AA: 30 subjects

N. Sub-study AB: 24 subjects

O. Sub-study AC: 24 subjects

P. Sub-study AD: 30 subjects

Q. Sub-study AE: 25 subjects

R. Sub-study AF: 20 subjects

*Note: 17 subjects from M.1 and 2 subjects from M.2 had been completed under 2011-0608. Therefore, total subject population for this protocol, 2016-0500, is 479.

The subject population will consist of young adults who have no psychiatric diagnosis. As we propose new sub-studies during the life of this new protocol, we will adjust the total number of subjects. Subjects who have a status relationship with the principal investigator may also be involved. These fall into two categories. One is post-doctoral and graduate students directly involved in the project and who will be authors of the publications reporting the results of the experiments. They may participate in situations in which they may find participation an important way for them to fine-tune the procedures and eventually interpret the results. The second category is individuals affiliated with the lab but not directly working on this study, who may wish to volunteer in a "moonlighting" capacity; that is, to earn money by being a research participant. Explicit policy of the laboratory forbids direct recruitment of status-relationship subjects falling under either category. We do not, however, forbid voluntary, self-initiated participation. In all cases, regardless of the circumstances of recruitment, participation as a subject will be entirely voluntary. One's choice with regard to participation in this study will in no way affect one's grades, evaluation, or position at the University of Wisconsin.

The subject population for each of the proposed repetitive TMS experiments will consist of 24 young adults. Our experience with several studies performed under protocol H-2003-033 and 2011-0608 has been that an initial recruitment of 24 subjects is necessary to yield a final N of 16. The reasons for this are varied; in some subjects, abnormalities from the MRI scan precludes further involvement, others meet exclusion criteria, as determined by the psychiatric interview; still others simply fail to participate in all stages of the experiment (common attrition). Our goal is to have 16 subjects in the final N of most sub-studies. In some cases, we may require more based on relevant literature or findings from pilot studies. This will permit us to directly compare the results from these sub-studies with those of Hamidi et al. (2009), the study from the PI's group that first characterized the individual differences in the effects of repetitive TMS on the EEG and on behavior. Because of its precedence, this experiment serves as the normative dataset against which the results of all the sub-studies proposed here will be compared.

We have not yet carried out a study with tCS, but our working assumption, based on careful reading of the literature and consultation with colleagues, is that the reasoning that we have applied to the design of TMS studies will also apply to tCS studies.

8. Procedures

8.A. Simultaneous TMS-fMRI study (involves sub-studies T.1 and T.2):

8.A.1. MRI Scan

In order to determine the stimulation sites, a T1-weighted 3D volumetric scan will be obtained from each subject prior to repetitive TMS administration. This will provide a structural map of each subject's brain. The map will enable a

3-dimensional reproduction of each subject's brain, which will be utilized for exact positioning of the TMS coil.

The procedures of the anatomical MRI will be the same as those approved for this PI in HS-IRB #2007-0075 and #2012-0652. There will be no TMS stimulation during this stage of the study.

8.A.2. TMS Motor Threshold (MT)

All TMS will be performed using a Magstim Super Rapid^2 Magnetic stimulator (Magstim Company Limited, Spring Gardens, Whitland, Wales, UK, http://www.jalimedical.com/rapid2.pdf) with two special nonferromagnetic TMS coils with a figure-8 design. For simultaneous fMRI/TMS stimulations, two 10 m shielded cables will connect the coil to the stimulator console positioned outside the scanner door.

The delivery of TMS pulses will be controlled by the fMRI console using a TTL pulse to trigger the Magstim stimulator *via* its external trigger interface. The pulses will be delivered 100 msec after an image acquisition, once every 20 sec; see below.

Single TMS pulses will be used to determine MT in each subject. MT is defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 μV in peak to peak amplitude) in a target muscle in 5 out of 10 trials using single pulse TMS administered to the contralateral primary motor cortex. MT is the standard in the field for determining the intensity of TMS (George et al., 1999). An authoritative set of safety guidelines for determining motor threshold is universally observed by researchers and clinicians who employ TMS – "Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-6, 1996" (Wassermann 1998). These guidelines specify the combined maximum levels of three stimulation parameters – intensity, rate, and duration – that have been demonstrated to be safe with human subjects. The guidelines published in (Wassermann 1998) (and subsequently reaffirmed in Rossi et al., 2009) indicate that an intensity of maximum stimulator output at a rate of 1 Hz for a duration of 5 sec falls within the safe range. Therefore, our method of beginning the MT determination procedure at 75% of stimulator output, possibly increasing intensity to as much as 100% of stimulator output, and delivering single TMS pulses at a rate no higher than .1 Hz (1 every 10 sec), falls within established norms for safe usage of TMS.

A "*safety certified*" member of the research team will be in the room with subjects during all TMS procedures. To qualify as *safety certified*, a member of the research team must undergo the following safety training: 1. Adult CPR and First Aid (American Red Cross OR American Heart Association Certified Courses and Instructor; 8 hour training). The CPR course teaches the skills of CPR, relief of an obstructed airway for victims of all ages, and rescue breathing including bag valve mask and barrier device. First aid will include emergency management of common acute medical situations. Both courses are intended for people who provide health care to patients in a wide variety of settings.

Written and skill testing is required. 2. Seizure identification and emergency management. (Epilepsy Foundation of South Central Wisconsin; 1.5 hour training.) The course will include education in seizure types and their typical presentations (aided by video clips); emergency management of seizures, and seizure first aid. This training will be completed with staff instructors from the Epilepsy Foundation.

These training certifications will be documented, and remain current while the personnel are involved with any of our studies. A full list of *safety certified* personnel will be a part of the "Key Personnel" list included in each Continuing Review report. Additionally, all additions to this list will be submitted to the HS-IRB via a Change of Protocol application.

In the event of a seizure or any other medical emergency during a research session, the policy will be the same as the UW Psychiatric Clinic, which operates in the same facility as our laboratory spaces. The policy states that the first response is to call 911 and administer appropriate first aid. This procedure is based upon recommendations from the Epilepsy Foundation of South Central Wisconsin and the American Red Cross. Following this, if no physician is in the room, a pre-designated physician who is in the building will be contacted.

Additionally, each of the research areas where human subjects are cared for will have postings of emergency procedures for seizures, as well as well-marked postings of emergency response numbers (e.g. 911). Additionally, a phone list for key personnel by cell phone will be available in these spaces.

8.A.3. Scanning

MRI studies will be performed on the 3 tesla MRI scanner (GE SIGNA, Milwaukee, WI) located in the Lane Family Neuroimaging Laboratory.

8.A.3.a. Positioning of the TMS coil

TMS coils will be mounted in the MR head coil (either a single coil or one coil on the right side and one on the left) with vitamin E capsules placed at the ends and center of each TMS coil to help locate its position in the structural images. Subjects will wear earplugs, and vision will be unconstrained. While lying on the gantry outside the scanner bore, the subjects will insert their heads into the MR head coil. Several vitamin E tablets will be affixed to the surface of each TMS coil to visualize placement within the MRI scanner. Vitamin E tablets are visible in MR images. Prior to scanning, the positions on the head surface for the initial coil placement will be estimated for the stimulated anatomic regions using the positioning apparatus and procedure described in section 4.D ("4. Potential Adverse Events, D. Positioning System") and the capsules will be fixed to the head surface. The subject will be positioned in the scanner and a high resolution 3D T1-weighted SPGR sequence will be run (the TMS device will be off) with a 1x1x2 mm voxel size (260x260x120 mm FOV with a 256x128x60 acquisition matrix). The acquisition time for the T1-weighted sequence is 3 minutes (using a 21 msec TR). The locations of the vitamin E tablets will be compared relative to

the desired anatomic regions desired for TMS stimulation. The amount of shift in the spatial position of the coil on the head surface will be estimated to center the coil over the desired anatomy. The subject will be moved out of the scanner bore, the TMS coil repositioned, the subject placed back in the scanner and the 3D T1-weighted scan will be repeated to ensure that the new coil position is correct. If a second position adjustment is deemed necessary, the subject will be moved out again, coil will be repositioned, followed by a third 3D T1-weighted image set.

8.A.3.b. Behavioral tasks for current, ongoing sub-studies

4. **Sub-study T.1. TMS-fMRI of the category-level representation of the UMI.**
   Sub-study T.1. will largely replicate the behavioral task of sub-study L.1. (two-item dual-retrocue task), using simultaneous fMRI rather than EEG. fMRI will provide higher spatial sensitivity and allow us to additionally use iterative LASSO (regularized regression for identifying voxels representing stimulus specific information) to identify parietal areas for TMS targeting. The study will be comprised of three sessions (a training session, TMS/fMRI session targeting IPS, TMS/fMRI session targeting LASSO-identified cortex).

5. **Sub-study T.2.**
   Sub-study T.2 will largely replicate the behavioral tasks of sub-study L.2. Training data will be generated from a scanning session during which 420 unique directions of motion and 420 unique colors are presented for 4 sec, each flashing at 1 Hz, with 8 stimulus-presentation epochs occurring serially to constitute a mini-block, and a 4-sec period at the end of each mini-block during which subjects indicate the number of speed/luminance changes they detected. During each mini-block, one randomly determined 4-sec epoch will be blank. (5 scans * 12-miniblock/scan * 84 stimuli/mini-block = 420 stimuli.) The 420 stimuli will be drawn at random, without replacement, from a set that is equally spaced around the 360° range of the stimulus space. The training session will comprise 10 7.2-min scans, with color and motion scans alternating during the course of the roughly 1 hr 20 min of EPI data acquisition. The experimental task will feature two conditions: *two-stimulus trials* and *one-stimulus trials*. On two stimulus trials, the targets will be a set of moving white dots, or a set of stationary colored dots. Subjects will then be cued as to whether direction or color will be probed. Subjects will then indicate whether or not a probe stimulus exactly matches the

cued dimension of the target. On *one-stimulus trials*, the targets will be the same, but the probe will be a single stimulus, presented centrally, comprised of dots appearing in one of the three colors and moving in one of the three directions. Subjects indicate whether the probe stimulus matches with regard to just the dimension specified by the target. The rationale is to quantify (with Forward Encoding Model fits) the dynamics of the "reactivation" effect found in sub-study L.1., and to measure TMS-evoked effective connectivity within the voxels that contribute to the representation of the UMI (using iterative LASSO as in sub-study T.1.), and between these voxels those that may maintain a top-down "pointer" to them.

8.A.3.c. Dosing of TMS

It has been demonstrated that TMS motor threshold in part depends on the distance from the coil to the underlying cortex, suggesting that dosing TMS should take into account the distance from scalp to cortex over the specific area to be stimulated (McConnell et al., 2001; Stokes et al., 2007). To achieve this, the distance from the scalp to the cortical target will be calculated with the frameless stereotaxic system that we use to guide the targeting of TMS (NexStim NBS), and any difference between this distance and the scalp-to-cortex distance for the location used to calculate MT will be corrected with the formula described by Stokes et al. (2007).

8.A.3.d. Experimental design

4. **Sub-study T.1.**
   The design: 3 (stimulus category: direction; face; word) x 2 (cueing: stay/switch) behavioral task. The IPS and the LASSO-identified targets will be in opposite hemispheres, and the latter will always be at least 5 mm distant from the nearest lip of the IPS. 108 trials per session yield 36 trials during which the critical stimulus category is a UMI. Single pulses of TMS, delivered at 110% of resting motor threshold intensity will be delivered on each trial during either the delay. Therefore, based on Guller et al. (2012), two scanning sessions will be required to generate a sufficient number of trials for each stimulation site.

5. **Sub-study T.2.**
   The design: The experiment will use the behavioral design of 3 (stimulus category: direction; face; word) x 2 (cueing: stay/switch). Iterative LASSO; FEM; and TMS-fMRI will be

involved. The rationale is to quantify (with FEM fits) the dynamics of the “reactivation” and to measure TMS-evoked effective connectivity within the voxels that contribute to the representation of the UMI (Interative LASSO), and between the voxels that maintain a top-down pointer to them.

8.A.3.e. TMS and fMRI acquisition

Functional imaging with TMS will be performed using an event related experimental design. The functional MRI pulse sequence is a standard pulse sequence that comes installed on the GE Discovery MR750 system, and is currently used by the PI of the present protocol for his on-going fMRI studies (PI: Postle; HS-IRB 2012-0652). EPI imaging parameters will be: TR = 2 seconds, TE = 30 msec, 64x64 acquisition matrix, 200x200 mm FOV, sagittal acquisition, 36 slices (4 mm thick with 0.5 mm gap) over the entire brain will be prescribed. During the acquisition period, subjects will watch a featureless black screen.

Neither single pulse TMS (i.e., less than or equal to 1 Hz), as employed in the simultaneous fMRI/TMS study) nor repetitive TMS require IDE approval because of the low risk associated with these techniques, as evidenced by their history of several years of incident free use in research by multiple centers around the world (e.g., Ashbridge, Walsh, & Cowey, 1997; Beckers & Hombert, 1991; Brandt, Ploner, Meyer, Leistner, & Villringer, 1998; Chen & al., 1997; Duzel, Hufnagel, Helmstaedter, & Elger, 1996; Epstein, 1998; Grafman & Wasserman, 1999; Hufnagel, Claus, Brunhoelzl, & Sudhop, 1993; Jahanshahi et al., 1998; Mottagh, Gangitano, Sparing, Krause, & Pascual-Leone, 2002; Muri, Vermersch, Rivaud, Gaymard, & Pierrot-Deseilligny, 1996; Oyachi & Ohtsuka, 1995; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Pascual-Leone et al., 2000; Ro, Cheifet, Ingle, Shoup, & Rafal, 1998; Walsh & Cowey, 2000; Wassermann, 1998).

8.B. Repetitive TMS and Single Pulse TMS study: involves sub-studies L.3, M.1, M.2

8.B.1. MRI Scan

In order to determine the stimulation sites, a T1-weighted 3D volumetric scan will be obtained from each subject prior to repetitive TMS administration. This will provide a structural map of each subject’s brain. The map will enable a 3-dimensional reproduction of each subject’s brain, which will be utilized for exact positioning of the TMS coil.

The procedures of the anatomical MRI will be the same as those approved for this PI in current HS-IRB 2012-0652. There will be no TMS stimulation during MRI scanning.

8.B.2. Determining individual alpha frequency (IAF) with EEG.

Each individual's EEG cycles at a slightly different rate, the so-called IAF. To measure this, a 60-electrode cap will be applied and connected to the TMS-compatible EEG amplifiers. The subject will then sit comfortably with her/his eyes open and closed for six alternating blocks of 30 sec each. (This is the typical procedure for measuring the alpha band component of the EEG signal, because alpha is strongest when the subject is resting and not engaged in task performance.) The resultant EEG data will be band-pass filtered to isolate components oscillating from 8-13 Hz, then submitted to a fast fourier transform (FFT) to determine at what frequency, within this range, the power is greatest. The frequency with the greatest power in the spectrum is the IAF.

8.B.3. TMS Motor Threshold (MT)

This will be identical to the procedure described for the *simultaneous TMS-fMRI study* under section 8.A.2., above.

8.B.4. Scanning

8.B.4.a. Behavioral Tasks

4. **Sub-study M.1. Comparing the effects of repetitive TMS delivered at multiple frequencies (MRI-guided) on visual short-term memory for the direction of motion.**
   Briefly, subjects will be asked to remember for short periods of time the direction of a group of dots moving (serial presentation). At the end of the delay period, a dial appears, and subjects will rotate the dial such that its line matches as closely as possible the direction of motion they had to remember. During the first session, subjects will be scanned in the fMRI while performing the task in order to identify the targets for subsequent rTMS. On a second day, behavioral tasks will be performed while recording EEG. Delay period rTMS will occur on two-thirds of the trials (10Hz, p=.5; or 20Hz, p=.5) with the remaining trials having no TMS. Stimulation will be applied on the middle temporal cortex (MT+) and intraparietal sulcus (IPS) on separate days. 10Hz is the frequency at which rTMS has been delivered on all of our previous studies and it is also the natural frequency of the posterior areas (including MT+) whereas 20Hz is the natural frequency of parietal areas (including IPS) as reported by Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M (2009) Natural frequencies of human corticothalamic circuits. J Neurosci.17;29(24):7679-85

5. **Sub-study M.2. Comparing the effects of repetitive TMS delivered at multiple frequencies (MRI-guided) on visual**

short term memory across stimulus dimensions.
This study will replicate sub-study M.1. with the exception that subjects will be remembering both directions of motion and colors. Depending on which item is tested, the probe will either be identical to sub-study M.1. (motion) otherwise the dial will be a color wheel that subjects adjust to match the cued target.

8.B.4.b. Positioning of the TMS coil

TMS will be performed in a clinic setting at the Wisconsin Psychiatric Institute and Clinic (WisPIC). For each subject, a digital 3D reconstruction of the subject's brain will be produced from the MRI data. After the subject is comfortably seated in a chair, s/he is fitted with a headband that contains fiducial markers that can be detected with an infrared camera. After these markers are calibrated with the 3D reconstruction of the brain scan, this 3D image moves on a computer screen, in real time, in precisely the same way as the subject's head (and, therefore, as her/his brain). The TMS coil is also detected by the infrared camera. When it is positioned over the subject's skull, a representation of the TMS coil and its zone of maximal stimulation can be viewed in relation to the brain. In this way, precise positioning of the TMS coil with respect to the brain can be achieved, and we will target specifically the regions described above. The TMS coil will be held by an articulating stabilizing arm that will hold the TMS coil rigidly in position when its stimulating position has been achieved. Note that this is the apparatus and procedure described in Section 4. D. ("4. Potential Adverse Events, D. Positioning System").

8.B.4.c. Dosing of TMS

In several previous studies performed under protocols H-2003-033 and 2011-0608, the PI's group has delivered trains of repetitive TMS at a rate of 10 Hz, with stimulator intensity 10 % above-motor threshold (Feredoes, Tononi et al. 2006; Postle, Ferrarelli et al. 2006; Feredoes, Tononi et al. 2007; Hamidi, Tononi et al. 2008; Hamidi, Tononi et al. 2009; Feredoes and Postle 2010). These stimulation parameters, together with a 5 sec inter-trial interval, fell within the safety guidelines for repetitive TMS (Wasserman, 1998; Rossi et al., 2009). Although we will stick to these parameters for some of the proposed studies, recent results obtained with these parameters (Hamidi et al., 2009) have created scientific reasons to vary these stimulation parameters systematically, as described above in **Sections 8.B.4.a.1 and 8.B.4.a.2.** Specifically, some of the proposed studies entail repetitive TMS at the frequency of sustained delay-period oscillatory power, which ranges across subjects from 10 Hz through 20 Hz, or at the natural frequency of the superior parietal lobule, which ranges across subjects from 18 Hz – 24 Hz. Following the published repetitive TMS

safety guidelines of Wasserman (1998), which were recently confirmed in a 10-year follow-up by the Safety of TMS Consensus Group (Rossi et al., 2009), repetitive TMS trains of between 10 Hz and 20 Hz, delivered at 110% of motor threshold, are considered safe if delivered for a duration not exceeding 1.2 sec (i.e., a total ≤ 24 pulses), and repetitive TMS trains of up to 25 Hz, delivered at 110% of motor threshold, are considered safe if delivered for a duration not exceeding 0.7 sec (i.e., a total ≤ 17 pulses). Note that these parameters also include an inter-train interval ≥ 5 sec. Thus, proposed studies featuring repetitive TMS delivered at a frequency greater than 10 Hz but ≤ 20 Hz will feature 1.2 sec-long stimulation trains, and studies featuring repetitive TMS delivered at a frequency of between 20 and 25 Hz will feature 0.7 sec-long stimulation trains. Another procedure that we would like to implement in our research skill is TBS which is another form of repetitive TMS that has been recently shown to be suitable for fMRI studies.

1. **Sub-study L.3**
Single-pulse TMS will be delivered at 90-110 V/m during the delay period between 2 and 3 seconds after the cue on each TMS present trial. Over the course of a 2 hour session, participants will receive a total of 540 pulses.

2. **Sub-study M.1**
Repetitive TMS will be delivered in 500 msec-long trains of 10 Hz (5 pulses/train) and 20Hz (10 pulses/train) at 90% of phosphene threshold, at the beginning of the delay period. There will be a minimum of 9-second interval between all trains.

3. **Sub-study M.2**
Repetitive TMS will be delivered in 500 msec-long trains of 10 Hz (5 pulses/train) and 20Hz (10 pulses/train) at 90% of phosphene threshold, at the beginning of the delay period. There will be a minimum of 9-second interval between all trains.

8.B.4.d. Experimental Design

1. **Sub-study M.1.**
Repetitive TMS trains at 10 Hz and 20Hz will be applied for 500 msec and delivered at 90% of phosphene threshold intensity during the delay period to MT+ and to IPS in separate sessions. There will be a 9 second interval between all trains.

Subjects will perform eighteen blocks (consisting of 34 trials) per stimulation site. (Total of 612 trials per stimulation site with 408 featuring repetitive TMS, 1/2 of these at 10Hz and 1/2 of these at 20Hz). The number of pulses that could be delivered on one stimulation site is maximum 3,060.

2. **Sub-study M.2.**
   The design will replicate M.1. with the exception that subjects will be asked to remember both directions of motion and colors.

TMS will be performed with a Magstim Super Rapid^2 Magnetic stimulator (Magstim Company Limited, Spring Gardens, Whitland, Wales, UK) equipped with a circular and a figure-8 coil. Triggering of the pulses will be initiated by the computer program presenting the stimuli to the subject. This program can be interrupted by the experimenter at any time. Neither single pulse TMS nor repetitive TMS (as proposed for the require IDE approval because of the low risk associated with these techniques, as evidenced by their history of several years of incident free use in research by multiple centers around the world (e.g., Ashbridge et al., 1997; Beckers & Hombert, 1991; Brandt et al., 1998; Chen & al., 1997; Duzel et al., 1996; Epstein, 1998; Grafman & Wasserman, 1999; Hufnagel et al., 1993; Jahanshahi et al., 1998; Mottaghy et al., 2002; Muri et al., 1996; Oyachi & Ohtsuka, 1995; Pascual-Leone et al., 1999; Pascual-Leone et al., 2000; Ro et al., 1998; Walsh & Cowey, 2000; Wassermann, 1998).

8.C. EEG-only: includes sub-studies O, U, V, Y, Z, AA, AB, AC, AD, AE, & AF

A separate set of EEG only experiments will build upon the questions and findings from previous sub-studies approved under this protocol and others from the PI (2012-0652), using new behavioral tasks that better assess questions answered using electroencephalography without fMRI or TMS. The procedure for these sub studies will be similar to those of Repetitive TMS studies (8.B.) except that there will be no initial fMRI session, and once subjects are fitted with an EEG cap, they will perform the behavioral tasks without the use of TMS procedures.

8.C.1.A. Behavioral tasks

1. **Sub-study O: Comparing biased-competition versus passive-decay models with EEG**
   This sub-study will replicate the procedure of approved sub-study J.2. the PIs fMRI IRB (2012-0652) using the same

behavioral task. The experimental task will begin with the presentation of a search target, drawn from the set of three stimulus types. After a delay, a “search array” comprising the target plus a second stimulus is presented. Both stimuli in the search array flicker, and each changes state a randomly determined 0-3 times during each trial. Subjects count the number of changes in the target image, ignoring changes in the nontarget image, and, at the offset of the array, report the number of target changes. MVPA will be performed on EEG data in an attempt to classify neural activity associated with the three stimulus categories and evaluate biased competition as a mechanism for changes in the decode-ability of these patterns.

2. **Sub-study U: Pre and post-training session EEG recordings**

   This sub-study performs pre and post-training sessions where subjects perform a number of tasks designed to measure various aspects of working memory and attention. The sub-study compares performance on these tasks after two different sets of training regimens to the performance before training. Electroencephalography (EEG) is used to record for the entirety of these sessions using the EGI Geodesic GES System 400 Sensor nets and the accompanying NetStation 4 software for data collection. Each of the two sessions, pre and post-training, last approximately 3.75 hours, with 2.25 hours of that spent engaging in the tasks and breaks given approximately every 9 minutes. Each session consists of seven different tasks testing differing aspects of working memory and attention. The tasks descriptions are below.

   #1. Digit Span: On each trial, a variable number of digits are presented one after another in the center of the screen. The subject’s job is to remember all the digits in the order they were presented. Between 1 and 12 digits are presented, and the subject is prompted to write down the digits he/she sees in order on the sheet, with an emphasis on accuracy.

   #2. N-Back: On each trial, the subject hears a letter and sees a bluesquare somewhere on the screen. On the one-back trials, the subject presses the “A” key only if the spoken letter is the same as the one on the previous trial. Additionally, the subject presses the “L” key only if the square is in the same position as on the previous trial. The subject only has a few seconds to respond, and the emphasis is on accuracy. After a variable number of trials, the subject is asked to report whether the

letter and/or square are the same as those presented two trials back (2-back). This applies for 3-back trials, 4-back trials etc.

#3. ANT: At the beginning of each trial, the subject sees a cross in the center of the screen. The subject focuses on the cross. After a period of time, either a single blue arrow head or a group of blue arrow heads appear either above or below the cross. In the single arrow condition, the subject hits the left arrow key as quickly as possible if the arrow is pointing to the left, and the subject hits the right arrow key as quickly as possible if the arrow is pointing to the right. In the group arrow condition, the subject hits the left arrow key as quickly as possible if the center arrow is pointing to the left. The subject hits the right arrow key as quickly as possible if the center arrow key is pointing to the right. In addition to the arrows, there are either one or two blue asterisks that appear near the cross right before the onset of the arrows. In the single asterisk condition, the arrow target eventually appears in the same position as the asterisk. In the double asterisk condition, the arrow target appears either above or below the cross. The cues help the subject to respond more quickly.

#4. PIMP: At the beginning of each trial, there is a white cross in the center of the screen. Four circles appear in the corners of the screen. Each circle will contain a number of moving dots. The focus is only on the red/blue circles. After a brief duration, the four circles disappear, and a single white circle with moving dots will appear in the center of the screen. If the dots in the white circle are moving in the same direction as the dots in one of the target circles (red/blue), the subject should hit the “1” key. If the white dots are moving in a different direction than the ones from the target, the subject should hit the “2” key. There are six blocks, each lasting about 8 minutes.

#5. OSPAN: At the beginning of each trial, there is a math problem on the screen. The task is to indicate whether or not the answer to the math problem is correct. If the answer is correct, the subject should hit the left arrow key. If the answer is incorrect, the subject should hit the right arrow key. Shortly after, the math problem is replaced with a letter. The subject should remember this letter. The subject receives anywhere between 1 and 7 of these math problems and letter combinations in a row. After a variable number of math problems, the subject must write down all of the letters that he/she recalls seeing in the previous trials in the order they were presented.

#6. Filtering: On each trial, the subject sees a display of colored lines. The display appears, disappears, and reappears. The task is to determine whether the red lines changed position from the first to the second display, focusing only on the red lines. A change in the red line position is indicated by clicking the right arrow key. No change in the red line position is indicated by the left arrow key.

#7. RAPM Pre (post version for post-test): A series of patterns on the screen appear, but a piece of the pattern is missing. The subject's task is to select the piece that he/she thinks best fits the pattern by pressing the corresponding number on the keyboard. The subject has 20 minutes to complete as many patterns as possible.

3. Sub-study V: (FREQMOD) Speed of alpha oscillations and temporal resolution of perception measured with EEG

This sub-study addresses the question of whether there is a correlation between the speed of individuals' alpha oscillations (measured with EEG) and the temporal resolution of their perception. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a two-flash fusion task. The task aims to determine the minimum time between two successive light flashes needed to perceive two, as opposed to one, distinct flashes. Subjects are seated 70 cm away from the monitor with a 100 Hz screen-refresh rate. Each trial begins with a central fixation cross (.98 degrees of visual angle) that reduces luminance to prepare subjects for the stimuli. The duration of the warning period is drawn from a uniform distribution between 1000 and 1500 ms. The fixation cross is present throughout the trial and the screen background is black. Grey disk stimuli are presented left or right of the fixation with equal probability and are always in the same location within a trial. Half of the trials are two-flash trials in which the first disk stimulus was present for 40 ms, followed by a blank screen of 10, 20, 30, 40 or 50 ms duration, followed by a 40 ms disk. The other half involves one-flash trials for which a single disk is presented. Subjects indicate whether they saw one or two flashes with a key press on a computer keyboard. The experiment takes 1.5 hours in total.

4. Sub-study Y: (2Back EEG) Tracking unattended memory representation in a 2-back task with EEG

This sub-study addresses the question of whether neural activity (measured with EEG) can be decoded to reveal the orientation of

objects that were briefly seen moments ago. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a two-back orientation recognition task. Each block consists of serial presentation of orientation grating stimuli (set of 6 possible orientations), with subjects indicating at each presented stimulus, starting at number 3, whether it matches that shown two stimuli ago. The goal will be to decode, using multivariate pattern voxel analysis (MVPA) and inverted encoding models (IEM), the neural activity associated with each of the 6 orientations, and to identify differences in activation when the memory report is accurate versus inaccurate. The experiment will take 2 hours in total.

5. Sub-study Z: (SPACEORDEREEG)
The aim of the study is to investigate the oscillatory and representational dynamics of contextual information in visual working memory. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a working memory orientation recognition task. Each block consists of serial presentation of orientation grating stimuli with subjects indicating their memory for those stimuli. The experiment will take 3-4 hours in total.

6. Sub-study AA: (SPACETIME EEG)
The aim of the study is to investigate how spatial and temporal expectation of forthcoming visual stimuli modulate both behaviour and brain oscillations. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a working memory orientation recognition task. Each block consists of serial presentation of orientation grating stimuli with subjects indicating their memory for those stimuli. The experiment will take 3-4 hours in total.

7. Sub-study AB: (LTM EEG)
The aim of the study is to shed light on the working memory-long term memory transfer mechanisms. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a working memory orientation recognition task. Each block consists of presentation of dot-motion stimuli with subjects indicating their memory for those stimuli. The EEG portion of the experiment will take 6-8 hours in total, split over two sessions, with an additional 1-hour behavioral session.

8. Sub-study AC: (DACOM)

The purpose of the study is to 1) investigate the trial-to-trial adaptive control of working memory in handling distraction from the discrimination stimuli, and 2) examine the neural correlates of the control processes in working memory, specifically testing the temporal and spatial characteristics of the control signal. EEG data are recorded from a Brain Products (brainproducts.com) actiCHamp Plus 64-channel high density EEG System while subjects complete a working memory dual-task paradigm. Each block consists of presentation of oriented Gabor patches, with an endogenous spatial cue indicating which of the two to memorize, and then they remember that orientation throughout the task, and recall the remembered orientation at the end of the trial. During the delay of the working memory task, another Gabor patch with varying levels of contrast will appear and participants will perform a psychophysical discrimination task on its orientation and report whether it is clockwise or counterclockwise compared to a vertical orientation. The experiment will take 3-4 hours in total.

9. Sub-study AD: (MFE)

The purpose of the study is to 1) find a neural marker of binding multiple features into VWM, and 2) investigate whether position information is an especially important feature for VWM binding. EEG data are recorded from a Brain Products (brainproducts.com) actiCHamp Plus 64-channel high density EEG System while subjects complete a typical visual working memory (VWM) task. Before memory array display, at the beginning of each trial, an arrow will be presented for 200 msec as a cue to notice either the left or right side of the memory array to be memorized. Four colored bars will be presented as the memory array then. The session will be separated into three block conditions to require participants to remember either Color and Orientation, Color and Position, or only Color in each block, respectively. At the end of each trial, one of the required features will be tested. All three blocks will be conducted with a counterbalanced order across participants. The experiment will take 3-4 hours in total.

10. Sub-study AE: (HAMS)

The purpose of this study is to find the neural mechanism whereby the irrelevant information is removed from working memory. EEG data are recorded from a Brain Products (brainproducts.com) actiCHamp Plus 64-channel high density EEG System while subjects complete a typical visual working memory (VWM) task. The participant will be required to make memory-based judgments of images in two tasks. The first task will include the presentation of three to-be-remembered oriented line patches with a memory judgment about one of the memory items after a brief delay period.

Patches may be presented sequentially or simultaneously, at the same location on the screen or at different locations across two conditions, and cued to be retained or dropped after a short delay in order to report the remembered orientation by adjusting a 180-degree dial. The second task will include the presentation of one patch and subjects will be asked to report the orientation of it after a delay. The experiment will take 4 hours total.

11. Sub-study AF: (PIII)

The purpose of the study is to investigate the ways in which prioritization of information in working memory protects its representation from interference to support more accurate behavior based on those memories. This study will test this directly both at the behavioral and neural levels. EEG data are recorded from a Brain Products (brainproducts.com) actiCHamp Plus 64-channel high density EEG System while subjects complete a typical visual working memory (VWM) task. The participant will be required to make memory-based judgments of images in two tasks. The first task will be a double-serial retrocue (DSR) task much like those typically used in the protocol's studies. The DSR task will involve the sequential presentation of two oriented patches. After a brief delay, a retrocue in the form of a digit ('1' or '2') will indicate which memory of the two oriented patches will be tested. After a longer delay of 4s, a test stimulus ('recall') will appear on the screen, which includes a line whose orientation can be adjusted by a trackball mouse to match the remembered orientation. To remind participants which item they are to recall, the retrocue digit will also re-appear on the recall display. After the participant makes their adjustment response, feedback will be provided by changing the color of the central fixation marker to green, yellow, or red, corresponding to small, mid, or large errors, respectively. Then, a second retrocue will appear that may be the same digit (50% of trials) or the other digit (50% of trials), followed by a shorter delay of 1s, and a second recall interval and feedback response. The second task will be comprised of 'neutral cue' trials that will serve as a control condition to understand the effects on performance of the meaningful retrocues. This task will be similar to the first portion of the DSR task with the sequential presentation of two oriented patches followed by a delay period. During the retrocue period, a '0' digit will appear to equate the task dynamics with the DSR task, but to be uninformative about which item will be tested. After the longer delay of 4s, the recall display will appear with a '1' or '2' digit indicating which item will be tested and the participant will make their adjustment as in the DSR task and receive feedback. At this point, the trial will end. The experiment will take 4 hours total.

8.D. tCS: includes sub-studies W and X

The sub-studies employing tCS are designed to address questions raised by the results of previous EEG studies in the lab, for example, Samaha et al., in press) and sub-study V, published as (Samaha and Postle, 2015).

8.D.1.A. Behavioral tasks

1. **Sub-study W: tACS study of the speed of alpha oscillations and temporal resolution of perception measured with EEG**
   This sub-study will replicate the procedure of approved sub-study V, using the same behavioral task. Subjects are seated 70 cm away from the monitor with a 100 Hz screen-refresh rate. Each trial begins with a central fixation cross (.98 degrees of visual angle) that reduces luminance to prepare subjects for the stimuli. The duration of the warning period is drawn from a uniform distribution between 1000 and 1500 ms. The fixation cross is present throughout the trial and the screen background is black. Grey disk stimuli are presented left or right of the fixation with equal probability and are always in the same location within a trial. Half of the trials are two-flash trials in which the first disk stimulus was present for 40 ms, followed by a blank screen of 10, 20, 30, 40 or 50 ms duration, followed by a 40 ms disk. The other half involves one-flash trials for which a single disk is presented. Subjects indicate whether they saw one or two flashes with a key press on a computer keyboard. The experiment takes 1.5 hours in total.

2. **Sub-study X: tCS of 2-choice orientation discrimination with confidence ratings.**
   On each trial a black and white grating stimulus will appear at the center of a computer screen for a short period (33 ms). The stimulus will either be tilted to the left or to the right of vertical by 45 degrees. The subject's task is to decide whether the grating was tilted to the left or right. Following this response, they will rate their confidence in their decision on a 1-4 scale using the computer keys. The experimental manipulation is whether tCS or sham tCS is applied over occipital-parietal cortex. Subjects will complete the task under both conditions, the order of which will be counter balanced. EEG will also be recorded from 6 occipital-parietal electrode sites. Prior to this main task a short (3 min) staircasing procedure will be run in

order to titrate the contrast of the grating stimulus to achieve task performance of ~75% accuracy. Total task time will be 1 1/2 hrs, which, with an estimated 30 minutes of setup, will result in ~2 Hrs of total experiment time.

9. **Inclusion and Exclusion Criteria**:

9.A. Inclusion Criteria:

1. Age of ≥ 18;
2. Right-handed;
3. Be in good health- determined by the investigator on basis of medical history, physical and neurological exam; for "EEG-only" sessions no physical or neurological exams will be performed;
4. Female subjects must attest to the fact that they are not pregnant on the day of the TMS procedures (by signing the relevant section of the consent form. This does not apply to "EEG-only" sessions;
6. Able to understand and speak English;
7. Able to provide written consent prior to admission.

9.B. Exclusion Criteria.

(Note: these are screened for by key personnel performing telephone screening and on-site screening (on day of the experimental session).

1. History of epilepsy, stroke, brain surgery, cranial metal implants, structural brain lesion, devices that may be affected by TMS (pacemaker, medication pump, cochlear implant, implanted brain stimulator) (physician evaluation and medical history);
2. Women who are breast-feeding (self-report)*;
3. History of head trauma with loss of consciousness for greater than 5 minutes;
4. Any history of seizures;
5. Any family history of seizures*;
6. Diabetes requiring insulin treatment*;
7. A serious heart disorder or subjects who have had a heart attack within the last 3 months;
8. Subjects who meet DSM-IV criteria for alcohol /drug abuse problems within the last six months;
9. Any current Axis I or II diagnoses or past Axis I diagnoses;
10. Required use of medication that affects CNS function;
11. A subject with metallic implants, such as prostheses, shrapnel or aneurysm clip-S, or persons with electronic implants, such as cardiac pacemakers. The magnetic field generated by the MR

machine can cause a displacement or malfunctioning of these devices*;
12. The female subject who is pregnant or planning to become pregnant;
13. The subject has had a diagnosis of cancer in the past 3 years and/or has active neoplastic disease;
14. The investigator anticipates that the subject will be unable to comply with the protocol.
15. Prohibited Concomitant Treatment: Any investigational medication; antipsychotic, antidepressant; or ECT; Other psychotropic medications including sedative hypnotics (excluding chloral hydrate zaleplon); sumatriptan (and similar agents); anxiolytics and herbals (e.g., St. John's Wort, Kava Kava); an introduction or change in intensity of psychotherapy; any non-psychopharmacologic drug with psychotropic effects (e.g., antihistamines, beta blockers).
17. Colorblindness
18. Poor or Uncorrected vision
19. History of fainting/syncope

* Denotes criterion that does not apply to "EEG-only" sessions.

In all instances in which a subject has been excluded from participation, we will discard all data from that subject relating to the reason for exclusion.

10. Study Evaluations.

10.A. Pre-Study Screening:

The Informed Consent will be reviewed and signed prior to any study procedures being completed. Individuals currently taking a psychoactive medication, will not be allowed to enter this study. The following procedures will be completed: MRI Screening Form and Health Screening Form. Information obtained from those who fail to pass the screening will not be retained. Following these assessments, the subject will be scheduled for the experiment at HERI. A technician will conduct a follow-up interview to inquire about the subjects' comments and concerns about the experimental procedure.

10.B. Efficacy Evaluations:

N/A

10.C. Safety Evaluations:

10.C.1. Safety will be monitored by reports of adverse events, vital sign measurements and lab evaluations. HERI is staffed by medical personnel and equipped with supplies for neurological monitoring (EEG), respiratory assistance (Ambu bag, oxygen tank and mask), and management of seizure (intravenous line materials, injectable anticonvulsant medication). A physician on call will be available at all times during testing. To prevent the risk of metallic objects being propelled by the magnetic field induced by the TMS device, metallic objects will be removed from the close vicinity of the device (< 10cm), as recommended by the manufacturer. This will include removing jewelry. Watches and magnetic sensitive devices (credit cards) will be kept at least 50 cm away from the coil.
The safety procedures in this protocol were drawn from the IFCN committee recommendations and studies of the safety of TMS (Wassermann 1998) and from a study of “tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men” (Anderson, 2006). Subjects will be screened for any history of seizure in themselves or family members (including febrile seizure), medications or conditions known to decrease seizure threshold (ETOH), implanted metallic objects or devices (e.g. pacemaker, TENS, cochlear implant, surgical clips), and any neurological or medical conditions.

10.C.2. Data Safety and Monitoring Plan

- Seizure induction is the type of adverse event that is explicitly captured under the monitoring plan; however, unanticipated adverse events that pose a serious physical risk to subjects are also included. Each *safety certified* member of the study team is responsible for alerting the PI (Postle) as soon as possible after the occurrence of a serious
- Adverse event.
- With regard to the “frequency of assessments/analysis of data or events captured by the monitoring plan,” this procedure is in place for each experimental session.
- The time frame for reporting an adverse event is as soon as possible once the safety and care of the subject has been addressed.
- The stop rule will be triggered by a single incidence of a serious adverse event.
- Unanticipated problems or adverse events will be reported to the HS-IRB per the IRB’s posted reporting policy.
- Adherence to the IRB-approved protocol is monitored weekly by the PI, via 1-on-1 meetings that he holds with each safety certified member of the study team who is actively running a sub-study.

10.D. Imaging: Adventitious Findings

A radiologist reviews all scans. Scans from all subjects are reviewed, although, if a study involves a series of scans within a 6-month period, only the 1st scan from a subject requires review. Dr. Howard Rowley has typically served as the radiologist overseeing the reading of scans for MRI studies. Clinically significant results will be reported to subjects no later than 37 calendar days from the day the imaging was completed (30 days for the reading of the image and 7 days are allowed from the date the image was read to contact the research participant). Subjects are given the option to have their physician informed of clinically significant findings as well.

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Appendix A: Seizure Identification and Emergency Management

Seizure Identification

There are many different types of seizures. People may experience just one type or more than one. The kind of seizure a person has depends on which part and how much of the brain is affected by the electrical disturbance that produces seizures. Experts divide seizures into generalized seizures (absence, atonic, tonic-clonic, myoclonic), partial (simple and complex) seizures, nonepileptic seizures and status epilepticus.

Generalized – Generalized seizures affect both cerebral hemispheres from the beginning of the seizure. They produce loss of consciousness, either briefly or for a longer period of time, and are sub-categorized into several major types: generalized tonic clonic; myoclonic; absence; and atonic.

Partial – In partial seizures the electrical disturbance is limited to a specific area of one cerebral hemisphere. Partial seizures are subdivided into simple partial seizures (in which consciousness is retained); and complex partial seizures (in which consciousness is impaired or lost). Partial seizures may spread to cause a generalized seizure, in which case the classification category is partial seizures secondarily generalized.

Partial seizures are the most common type of seizure experienced by people with epilepsy. Virtually any movement, sensory, or emotional symptom can occur as part of a partial seizure, including complex visual or auditory hallucinations.

- **Simple -** People who have simple partial seizures do not lose consciousness during the seizure. However, some people, although fully aware of what's going on, find they can't speak or move until the seizure is over. They remain awake and aware throughout. Sometimes they can talk quite normally to other people during the seizure. And they can usually remember exactly what happened to them while it was going on. However, simple partial seizures can affect movement, emotion, sensations, and feelings in unusual and sometimes even frightening ways.
- **Complex -** Complex partial seizures affect a larger area of the brain than simple partial seizures and they affect consciousness. During a complex partial seizure, a person cannot interact normally with other people, is not in control of his or her movements, speech or actions; cannot control what he or she is doing; and does not remember afterwards what happened during the seizure.
- **Non-epileptic –** Non-epileptic seizures are episodes that briefly change a person's behavior and often look like epileptic seizures. The person having non-epileptic seizures may have internal sensations that resemble those felt during an epileptic seizure. The difference in these two kinds of episodes is often hard to recognize by just watching the event, even by

trained medical personnel. But there is an important difference. Epileptic seizures are caused by abnormal electrical changes in the brain and, in particular, in its outer layer, called the cortex. Non-epileptic seizures are not caused by electrical disruptions in the brain.

Status Epilepticus

Most seizures end after a few moments or a few minutes. If seizures are prolonged, or occur in a series, there is an increased risk of status epilepticus. The term literally means a continuous state of seizure and is considered a medical emergency. Status Epilepticus is defined as 30 minutes of uninterrupted seizure activity. An estimated 42,000 deaths and thousands more instances of brain damage per year follow episodes of status. Status epilepticus is most common in the very young and the very old, with the lowest incidence at ages 15-40.

Seizure Management

Convulsive Seizure

For individuals that experience generalized seizures, the following first aid should be provided in order to assure safety for all individuals involved and nearby.

- Keep calm and reassure onlookers.
- Don't hold the person down or try to stop his movements.
- Time the seizure with your watch.
- Clear the area around the person of anything hard or sharp.
- Loosen ties or anything around the neck that may make breathing difficult.
- Put something flat and soft, like a folded jacket, under the head.
- Turn him or her gently onto one side. This will help keep the airway clear. Do not try to force the mouth open with any hard implement or with fingers. It is not true that a person having a seizure can swallow his tongue. Efforts to hold the tongue down can injure teeth or jaw.
- Don't attempt artificial respiration except in the unlikely event that a person does not start breathing again after the seizure has stopped.
- Stay with the person until the seizure ends naturally.
- Be friendly and reassuring as consciousness returns.
- Contact on-call physician.
- If, at the discretion of the physician, the subject does not require admission to a hospital, accompany him/her to his/her home to insure that he/she arrives safely.

Non Convulsive

For individuals that experience non-convulsive, the following first aid should be provided in order to assure safety for all individuals involved and nearby.

- Watch the person carefully and explain to others what is happening. Often people who don't recognize this kind of behavior as a seizure think that the dazed person is drunk or on drugs.
- Speak quietly and calmly in a friendly way.
- Guide the person gently away from any danger, such as a steep flight of steps, a busy highway, or a hot stove. Don't grab hold, however, unless some immediate danger threatens. People having this kind of seizure are on "automatic pilot" so far as their movements are concerned. Instinct may make them struggle or lash out at the person who is trying to hold them.
- Stay with the person until full consciousness returns.
- Contact on-call physician.
- If, at the discretion of the physician, the subject does not require admission to a hospital, accompany him/her to his/her home to insure that he/she arrives safely.

Appendix B: Completed Studies Category A

1. Sub-study A: The role of parietal regions as sources of attentional control for spatial attention and spatial working memory.

The purpose of this study is to test the hypothesis that single pulses of TMS delivered to the superior parietal lobule (SPL) and intraparietal sulcus (IPS), areas implicated in the control of attention, will alter posterior task-related activity in a similar way for spatial delayed recognition as they do for spatial attention. More specifically, we predict that when subjects are attending to a location of space to, for example, the left of central fixation, the response evoked by a single pulse of TMS will be greater in magnitude in visual regions in the right hemisphere than in the left. The same pattern is predicted when subjects are remembering the locations of stimuli that had been presented to the left of fixation at the beginning of a delayed-recognition (i.e., “working memory”) task. Study A will combine a delayed-recognition task with a variant that requires spatial attention rather than spatial working memory. In the delayed-recognition task subjects will be presented with four dark-gray shapes appearing serially in four different locations on the (lighter gray) screen. The center of the screen is marked with a cross on which the subjects must keep their eyes throughout the trial. The stimuli are followed by a 8 second delay period, during which, on half of the trials, TMS is delivered. Finally, a white circle appears on the screen, and subjects indicate with a button press whether or not this probe appears in the same location as had one of the four shapes. In the spatial attention task, the fixation cross will rotate so as to point, throughout the delay period, to the location on the screen to which the subject should attend in order to detect a briefly presented, faint target that will appear with an unpredictable latency. The single pulse of TMS will be delivered with the same timing during both the working memory task and the attention task. During the inter-trial interval (ITI), the subject will perform a visuomotor tracking task that requires moving a cursor so that it stays on top of a moving target stimulus. The subject moves the cursor by pressing directional keys on a keypad. Performance is measured as the error between the position of the target and position of the cursor, as well as of the velocity of the cursor (e.g., if it stops moving).

Experimental Design: The design, 3 (task: attention; delayed recognition; no task) x 2 (visual field) x 2 (TMS: present, absent) factorial (modified to exclude empty and nonsensical cells), yields blocks/scans of 18 trials each. Single pulses of TMS, delivered at 110% of resting motor threshold intensity will be delivered to the right SPL, right IPS, and right postcentral gyrus (PoCG, a control area selected because it is not involved in the cognitive constructs under investigation). Stimulation will be blocked by region, with the order counterbalanced across subjects, with 3 consecutive blocks per region. (Total of 162 trials, 81 featuring TMS; therefore, total of 81 pulses delivered per experiment. Because trials are randomized with respect to whether or not a TMS pulse is delivered, the minimum time between pulses will be 18 sec (when pulses are delivered on two consecutive trials).)

2. Sub-study B.

Is the source of *object-based* attentional control the same for nonmemory attention tasks as for working memory tasks?

The attention task will present a flickering (750 msec on, 250 msec off) shape of approximately 1 degree of visual angle at central fixation, and the subject's task is to indicate with a button press each time a feature of the shape changes. Shapes will be drawn from a set of polygons that have been normatively determined to be difficult to verbalize, and have been used in several of the PI's studies of object working memory. There are 4 variants of each shape, each of which differs by just one salient feature, and changes among the 4 will occur unpredictably an average of 3 times (range = 1 – 5) per trial. The delayed-recognition task will draw from the same pool of stimuli as the attention task, with invalid probes drawn from one of the 3 variants of the target shape from that trial. The regions to be targeted will be the frontal eye fields (FEF), a region previously targeted in two studies conducted under protocol H-2003-033, and the region from sub-study A that provide the most robust results, plus the leg area of somatosensory cortex in the postcentral gyrus (PoCG), an area used as a stimulation control area in many of the studies completed under protocol H-2003-033. During the inter-trial interval (ITI), the subject will perform a visuomotor tracking task that requires moving a cursor so that it stays on top of a moving target stimulus. The subject moves the cursor by pressing directional keys on a keypad. Performance is measured as the error between the position of the target and position of the cursor, as well as of the velocity of the cursor (e.g., if it stops moving).

Experimental Design: The design, 3 (task: attention; delayed recognition; no task) x 2 (visual field) x 2 (TMS: present, absent) factorial (modified to exclude empty and nonsensical cells), yields blocks/scans of 18 trials each. Single pulses of TMS, delivered at 110% of resting motor threshold intensity will be delivered to the right FEF, right SPL or IPS, and right PoCG. Stimulation will be blocked by region, with the order counterbalanced across subjects, with 3 consecutive blocks per region. (Total of 162 trials, 81 featuring TMS; therefore, total of 81 pulses delivered per experiment. Because trials are randomized with respect to whether or not a TMS pulse is delivered, the minimum time between pulses will be 18 sec (when pulses are delivered on two consecutive trials).)

3. Sub-study C.

Further investigation of the mechanisms of *object-based* attentional control and its relation to object working memory.

The logic will be to cross two stimulus types – faces and houses – with two task types – attention and working memory. Tokens of the two stimulus types will always be presented superimposed at central fixation, a procedure that has been used to demonstrate that object-based attention can selectively bias activity in regions associated with processing either stimulus type, depending on task instructions. The responses evoked by TMS pulses during task performance will ascertain whether the targeted regions are a source of object-

based attentional selection by indicating whether TMS pulses have differential effects on face-selective vs. house-selective cortex as a function of task instructions. The regions to be targeted will be the same as those from Study B. During the inter-trial interval (ITI), the subject will perform a visuomotor tracking task that requires moving a cursor so that it stays on top of a moving target stimulus. The subject moves the cursor by pressing directional keys on a keypad. Performance is measured as the error between the position of the target and position of the cursor, as well as of the velocity of the cursor (e.g., if it stops moving).

Experimental Design: The design, 3 (task: attention; delayed recognition; no task) x 2 (visual field) x 2 (TMS: present, absent) factorial (modified to exclude empty and nonsensical cells), yields blocks/scans of 18 trials each. Single pulses of TMS, delivered at 110% of resting motor threshold intensity will be delivered to the three from sub-study B. Stimulation will be blocked by region, with the order counterbalanced across subjects, with 3 consecutive blocks per region. (Total of 162 trials, 81 featuring TMS; therefore, total of 81 pulses delivered per experiment. Because trials are randomized with respect to whether or not a TMS pulse is delivered, the minimum time between pulses will be 18 sec (when pulses are delivered on two consecutive trials).)

4. Sub-study D. Comparing the effects on spatial working memory of repetitive TMS delivered at multiple frequencies (MRI-guided)

This study modifies the procedure of the working memory task from *sub-study A* by shortening the delay period to 3 sec, simultaneously recording the EEG, including three EEG sessions, and varying the frequency at with repetitive TMS is delivered, so as to compare the effects of repetitive TMS delivered at 10 Hz, IAF+1Hz, and the frequency of sustained delay-period oscillatory power in the 10 - 20 Hz range. In this sub-study subjects will be presented with four dark-gray shapes appearing serially in four different locations on the (lighter gray) screen. The center of the screen is marked with a cross on which the subjects must keep their eyes throughout the trial. The stimuli are followed by a 3 second delay period, during which, on half of the trials, repetitive TMS is delivered. Finally, a white circle appears on the screen, and subjects indicate with a button press whether or not this probe appears in the same location as had one of the four shapes. The three frequencies are of interest for varying reasons: 10 Hz is the frequency at which repetitive TMS has been delivered on all of our previous studies of spatial working memory, and comparison of results with the other two frequencies vs. the “gold standard” of 10 Hz will thus be very informative. IAF+1 Hz is the frequency at which Klimesch et al. (2003) have reported facilitatory effects of repetitive TMS, and offers a parameter by which repetitive TMS frequency can be tailored to the physiology of individual subjects. Sustained delay-period oscillatory power has been observed in many published EEG studies, including *Hamidi, M., Slagter, H.A., Tononi, G., and Postle, B.R. (2009). Repetitive transcranial magnetic stimulation affects behavior by biasing endogenous cortical oscillations. Frontiers in Integrative Neuroscience, 3:14. doi:10.3389/neuro.07.014.2009. PMC2707056.* Thus, it offers a second task-

related parameter by which repetitive TMS frequency can be tailored to the physiology of individual subjects. As indicated above, the sub-study will include three EEG sessions. The first will be the brief “eyes open/eyes closed” session to determine IAF, the second will entail repetitive TMS at 10 Hz and at IAF +1, the third, repetitive TMS at 10 Hz and at the frequency of sustained delay-period oscillatory power. The reason for using 10 Hz during two sessions is that although previous studies have revealed individual differences in the effects of repetitive TMS on both behavior and task-related EEG (Hamidi et al., 2009; Sub-study L), we do not yet know whether these patterns of individual differences are stable over time. That is, if 10 Hz repetitive TMS produces an increase in alpha-band power and a decrease in accuracy for subject #1, and a decrease in alpha-band power and an increase in accuracy for subject #2 (mirroring what we saw in Hamidi et al (2009)), will these same two subjects show similar effects if they perform the same experiment on a different day? In other words, what is the test-retest reliability of our procedure? The third session will occur on a different day than the second.

Experimental Design: Repetitive TMS will be delivered in 1.2 sec-long trains of 10 Hz, IAF +1, and sustained delay-period oscillatory power, at 110% of the resting motor threshold intensity, at the beginning of the delay period. There will be a 5 second interval between all trials.

5. Sub-study E. The effects on spatial working memory of repetitive TMS delivered at a region’s natural frequency (MRI-guided)

The natural frequency of a corticothalamic circuit is the frequency with which a brain region oscillates when stimulated by a pulse of TMS (analogous to the “ringing” that results from striking a bell, Rosanova et al., 2009). For the superior parietal lobule (SPL) this corresponds to 20 Hz. The SPL has been the target of most of our previous repetitive TMS studies of spatial working memory, and 10 Hz repetitive TMS of the SPL has produced interesting behavioral and EEG results (i.e., Hamidi et al., 2008; 2009). The purpose of this sub-study is to compare the results of repetitive TMS of SPL at 10 Hz with those of repetitive TMS of SPL at this region’s natural frequency, which can vary between 18 – 24 Hz depending on the individual. At issue is whether the natural frequency reflects a functional property of a region, or whether it is merely a byproduct of a region’s corticothalamic architecture that does not influence that region’s function. The procedure for Sub-study E will replicate that of Sub-study D, with the exceptions that there will be two sessions (instead of 3; Session 1 will entail IAF estimation and natural frequency estimation, and Session 2 will entail task performance), and repetitive TMS will be delivered concurrent with behavioral task performance at IAF +1 and at the subject’s natural frequency.

Experimental Design: Depending on the natural frequency of SPL for a given subject, all repetitive TMS trains will be delivered for either 1.2 sec (if natural frequency ≤ 20 Hz) or 0.7 sec (if natural frequency > 20 Hz and ≤ 25 Hz), at frequencies of IAF+1Hz and of the subject’s natural frequency, at 110% of the

resting motor threshold intensity, at the beginning of the 3 sec-long delay period. There will be a 5 second interval between all trials.

6. Sub-study F. The effects of cognitive training on sustained delay-period brain activity.

Analyses of data from two previous studies performed by the PI's group under protocol H-2003-033 indicate that there are considerable individual differences in the patterns of sustained delay-period oscillations as measured by EEG. The nature of these differences is intriguing, because they are present despite the fact that all subjects are performing the same task, and are generally doing so at the same level of proficiency. They raise such question as: *Do these differences underlie individual differences in behavior? Do they reflect differences in the cognitive processes engaged by different individuals, or, instead, perhaps differences in trait-like physiological profiles that do not relate directly to task performance?* Answers to these questions will contribute importantly to understanding which elements of sustained delay-period oscillations are critical for working memory-task performance. The strategy for addressing these questions, to be implemented in this sub-study, will be twofold: a) administer several psychometric tests that measure important cognitive and affective traits, and evaluate which covary with sustained delay-period oscillations; and b) assess the effects on sustained delay-period oscillations of a 5 week-long course of cognitive training on a working memory task. Previous work indicates that such training can produce improvement on working memory-task performance that generalizes to other cognitive domains (e.g., Olesen et al., 2004). Our question will be which, if any, aspects of sustained delay-period oscillations are also sensitive to cognitive training. Thus, there are three categories of behavioral task in this sub-study: the *EEG* and *TMS-EEG tasks* during which sustained delay-period oscillations are measured, the *psychometric tasks*, and the *training task*.

a) *EEG and TMS-EEG*. The EEG recording session will proceed in four blocks, each comprising 150 trials. For *Block 1*, subjects will perform a spatial delayed-recognition task (similar to those conducted under H-2003-033), in which either 2 or 4 squares are presented serially in to-be-remembered locations in a pre-cued quadrant of the screen, followed by a delay period of 3750 msec, followed by the onset of a circle that either does or does not (with equal probability) appear in one of the cued locations. For the three subsequent blocks the task will be repeated, but in *Block 2*, two pulses of TMS will be delivered during the delay period (this TMS procedure will be identical to the one previously approved by the HS-IRB under protocol fH-2003-033); in *Block 3*,

irrelevant (i.e., *not* to be remembered) squares will be presented in an uncued quadrant of the screen at the same time as the to-be-remembered squares; and in *Block 4*, irrelevant (i.e., *not* to be remembered) squares will be presented during the delay period of the trial.

b) *Psychometric tasks.* Each of these has been selected to estimate a psychological construct believed to related to working memory-task performance.

i) Change Detection. This task is frequently used to estimate "visual short-term memory [VSTM] capacity" (e.g., Vogel & Machizawa, 2005). After a 200 ms fixation plus a cue to covertly attend to either the left or right visual hemifield, a target memory array of randomly colored squares is presented for 100 ms with set sizes of 3, 4, 6, or 8 items. Subjects remember the target colors in the cued hemifield and ignore the other field. Following probe array, subjects indicate match versus non-match with button press.

ii) Precision Task (Bays & Husain, 2008) - This task will assess the precision with which an item's orientation is remembered. An array of colored bars is presented in one hemifield for 1000 ms during which the subject covertly attends to the array while maintaining fixation. Following a 500 ms delay, a probe appears in the same or different orientation as one of the stimulus bars. Probe duration is 250 ms following which the subject must indicate whether or not there was an orientation change.

iii) Operation Span task: This is a standard test to assess "working memory capacity" (Turner & Engle, 1989) Serial presentation of stimuli (letters) is interleaved with arithmetic problems that subjects must solve as they are presented. The task ends unpredictably, after varying numbers of letters are presented, with a cue requiring recall of the order of the letters

iv) Sustained attention task. (Demeter et al., 2008). Subjects fixate on the center of the screen and report if they perceived the stimulus after probe tone. On 50% of trials the stimulus, a small gray box, will flash at fixation. A distractor condition

adds a flashing background to the baseline task making the target less distinguishable.

v) Guided search: This task probes ability to control attention via internal representations (e.g., Gold et al., 2007). Subjects see a template shape (a bracket oriented up, down, left, or right). Next, an array of similar items (distractors) and one template match are presented. Subjects search the array for a match and indicate if a match exists. The task is "guided" via internal representation of the target. RT and accuracy will be measured. Difficulty is varied by the set size (4,8,12, or 16 distractors).

vi) Stroop Task (Stroop, 1935): This is a classic test assessing selective attention, cognitive flexibility, and processing speed. Subjects name the color in which words are presented, with difficulty increased when, e.g., the word "red" is presented in blue ink.

vii) Attention Control Scale: This 20-question inventory quantifies self-reported ability to control attention through assessment of attention focusing and flexibility (for example multitasking; Derryberry and Reed, 2002; Derryberry and Rothbard). Typical items include "When concentrating I ignore feelings of hunger and thirst". Subjects report how often they agree with the statement on a 4-point scale. The inventory is self-paced.

viii) Raven's Advanced Progressive Matrices (Raven et al., 2003): This is a nonverbal test to assess the construct of "general fluid intelligence" (gF). Each matrix problem is a set of eight pictures, arranged in a 3 x 3 grid with the last picture missing. The order and design of the given pictures follows a rule. Subjects deduce the rule and choose the last image from a set of 8 options. The test consists of a set of 36 problems in increasing order of difficulty, administered via paper and pencil. Subjects solve as many matrix problems as possible within 40 minutes.

ix) Spielberger State-Trait Anxiety Inventory (STAI-X2, Spielberger et al., 1983) is a common measure of trait-like individual differences in non-clinical anxiety (i.e., it is not designed to assess clinical anxiety disorder). This 20-question inventory determines if a person has anxiety as a

trait (versus a state - STAI-X1). Typical items include “I feel secure” and “I wish I could be as happy as others seem to be” where the subject rates how often the statement is applicable.

x) BIS/BAS (Behavioral inhibition system/ activation system) - This widely employed 24-item questionnaire assesses behavioral inhibition and activation (Carver & White, 1994). The BIS is postulated to regulate aversive motivational behavior towards environmental factors such as punishment and inhibits movement towards a goal. Typical BIS questionnaire items include “Criticism or scolding hurts me quite a bit”. The BAS system is postulated to control appetitive behavior regulated by dopamine systems. Typical BAS questionnaire items include “I go out of my way to get things I want”. The subject indicates how much they agree or disagree with the statement.

xi) Bartlett Impulsivity Scale (BIS-11, Patton et al., 1995). This is a 30-item inventory to assess impulsive traits. Impulsiveness is broken down into first order factors including attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability. Representative items include “I am a careful thinker”. Items are scored on a 4 point scale where 1=rarely to 4=always. Scale reliability has been confirmed, and the inventory has been reassessed to accommodate updated findings in the field.

xii) Personality Research Form E: This 20-question inventory is widely used for assessing personality traits including impulsivity, aggression, autonomy, and nurturance (Jackson, 1974).

c) *Training Task*. The training task will be an adaptive spatial n-back task (Olesen et al., 2004), in which subjects view a 4 x 4 grid, stimuli are presented serially in different cells (duration = 500 msec, interstimulus interval = 2500 msec, 1 trial is 3000 ms) and subjects indicate for each whether the current stimulus appears in the same location as had the stimulus n items previously. (E.g., in the 1-back condition, subjects compare the current item to the previous one, in the 2-back condition, they compare the current item to the item-before-last, etc.) The task is adaptive in that the n varies

as a function of performance, according to the following algorithm: there are 20 trials per block, performance > 90% will increase the n-level, performance on 3 consecutive blocks that are < 50% will decrease the n-level. Each day, the sessions start at n = 2. Subjects will perform this task for 40 min per day, M-F, for 5 consecutive weeks. Subjects can take a break every 10 blocks. Training will be performed in the PI's laboratory at the Brogden Psychology building.
Experimental Design: 2 pulses of TMS will be delivered at 110% of MT during the delay period. The timing of the first pulse will be jittered relative to the onset of the delay period, and averaging a latency of 750 msec (+/- 250) for the first pulse and 2000 msec for the second pulse relative to the onset of the delay period. The interval between pulses will be jittered, and will average 1250 msec.

7.Sub-study G. The effect of repetitive TMS using theta burst stimulation on spatial working memory as measured by fMRI-EEG. Behavioral tasks will be performed during fMRI scanning and will be similar to those approved as sub-study G under the PI's protocol HS-IRB #2012-0652. Briefly, subjects will be asked to remember for short periods of time (8 seconds) the direction of a group of dots moving. On any given trial, one, two, or three of the dot patterns can be moving. At the end of the delay period, a dial appears, and subjects will rotate the dial such that its line matches as closely as possible the direction of motion of the color-matching dot pattern. During the first day's scanning session, subjects will perform 180 trials across six runs. On a second and third day, there will be a break after the first three runs and repetitive TMS using TBS will occur, before running the last three runs. A short perceptual task will also be added on each day to control for potential perception modification in the encoding phase and it will be done before the main task.

The **aim** of this study is to explore the neural mechanisms underlying findings from previous fMRI studies by the PI's group. In Riggall and Postle (2012), we showed that the contents of a single item held in visual short term memory (STM) can be decoded from sensory visual cortex, despite the fact that these areas do not exhibit elevated, sustained activity. In Emrich SM, Riggall AC, Larocque JJ and Postle BR (2013), we confirmed these results, and also discovered showed that the neural representations changes as a function of load, in manner that corresponded to load-dependent declines in mnemonic resolution. Thus, the aim of this sub-study is to better understand how these visual

representations and related brain circuits are disrupted as a result of TBS of a given brain area (i.e., middle temporal visual cortex – MT and inferior parietal sulcus - IPS). More specifically, we would like to investigate how item-specific and load-specific visual STM representations are affected by the perturbation of different brain areas involved in working memory. Lee and D'Esposito (2012) stimulated the prefrontal cortex (PFC) with TBS before a working memory task, and showed that PFC disruption decreased the tuning of extrastriate cortex responses, coinciding with decrements in working memory performance. They also found that activity in the homologous PFC region in the nonstimulated hemisphere predicted performance following disruption (i.e., participants with greater homologous PFC activity and greater connectivity between this region and extrastriate cortex were the most resistant to PFC disruption). What if we directly stimulate the sensory cortex which holds the visual representation of the visual STM (versus the parietal lobe)? Our main hypothesizes would be that after TBS of occipital cortex (i.e., MT area known to be involved in motion), there will be a decrement in behavioral responses and a decreased memory representation in the visual cortex, which might most strongly affect the high memory load trials. After TBS of parietal cortex (i.e., IPS known to be involved with the load), we might expect to also have a decrease of behavioral responses (probably with high load) but the representation of the information per se in the visual cortices should stay the same, confirming a role for attentional control, but not stimulus representation, per se, in this region.

Experimental Design: TBS is an innovative non-invasive repetitive TMS technique that has been recently shown to have several advantages over the conventional repetitive TMS. First, the conventional repetitive TMS can induce performance-enhancing or performance-impairing effects for any given individual, which creates variability in the data. Second, at present, conventional repetitive TMS cannot be used during fMRI scanning due to a number of practical considerations. In particular, the heating of the TMS coil, which builds up over repeated high-frequency trains, would pose a complication. Outside of the fMRI lab, an air-cooled system counteracts this, but this apparatus does not fit inside the bore of the magnet. Thus, a repetitive TMS protocol inside the scanner would need to incorporate periodic lengthy pauses to allow the cooling down of the coil. Third, applying conventional repetitive TMS before fMRI scanning, in a

manner comparable to what we are proposing to do with TBS, the effects would be short lasting (usually 15 minutes or less) and often weak and highly variable (Gangitano et al., 2002). TBS is therefore ideally suited for studying the effects of repetitive TMS with fMRI because of its rapid and safe administration as well as its robust and less variable responses across populations of subjects. We propose to use a **continuous TBS** protocol that consists of 50 Hz trains of three TMS pulses repeated every 200 ms continuously over a period of 40 seconds (600 pulses total). Continuous TBS has been shown to depress activity in the stimulated brain region for up to 60 minutes following stimulation (Huang et al., 2005, 2009). The TBS procedure will be the same as in previously published studies (Huang et al., 2005, 2009; Lee and D'Esposito, 2012; Andoh and Zatorre, 2012; Morgan et al, 2013) and will follow the established safety guidelines (Rossi et al, 2009; Oberman et al, 2011). The risk of adverse events during TBS is comparable to or less than the other conventional high frequency repetitive TMS protocols (Rossi et al 2009, Oberman et al, 2011).

8.Sub-study H. Comparing the effect of repetitive TMS on items inside and outside of the focus of attention. This study replicates procedures from Zokaei et al. (2013) where 4 pulses of 20Hz rTMS at 60% of stimulator output was shown to abolish any recency effect from serial presentation and even improve performance on non-privileged items. In addition, these parameters are applied to dual retrocueing paradigms previously used by Dr. Postle's group. Experiment 1 will replicate the Zokaei et al. (2013) design. Experiment 2 will use the same task with modified timing. Experiment 3 will test the attentional retrocueing paradigm. Experiment 1 will measure only the behavioral effects of rTMS, while both experiments 2 and 3 will be carried out while simultaneously collecting EEG data. All subjects will undergo a functional localizer in the MRI (fMRI) during the 1st session (behavioral neurological testing and MRI) to identify optimal motion sensitive target locations in MT+. In all studies we will be including an active control where the same TMS parameters are applied to primary somatosensory cortex.
Experimental Design: 4 pulses of 20Hz rTMS (150ms train) will be delivered at 110% of adjusted motor threshold (Stokes et al., 2005) to motion sensitive areas of MT+ (identified by functional localizer task) or primary somatosensory cortex (S1). The task structure is such that there is never less than 5000ms between trains.

Experiment 1: Subjects will view 2 random dot kinematograms (RDKs) presented serially (300ms

each) at fixation (one red, one green). The center of the screen is marked by a white cross on which subjects must maintain fixation throughout the trial. The stimuli are each followed by a mask and then a delay. On half of the trials, TMS is applied delay following either the 1st or 2nd RDK and mask. The second delay is followed by a response probe consisting of a circular aperture and a radial line (either red or green) indicating which stimulus to respond to. The subjects are instructed to adjust the line until it points in the same direction as the motion in the indicated RDK stimulus.

Experiment 2: This task will be identical to Experiment 1 with the exception that the timing will be changed to allow for spectral-power EEG analyses.

Experiment 3 (2 sessions): Subjects will view 2 random dot kinematograms (RDKs) presented serially (300ms each) at fixation (one red, one green). The center of the screen is marked by a white cross on which subjects must maintain fixation throughout the trial. The stimuli are each followed by a mask and then a delay. The fixation cross will then either turn red or green indicating a retrocue as to which stimulus will be probed Retrocues are always 100% informative. TMS is then applied during the delay period following the first retrocue on half of the trials. A subset of trials will then probe the cued stimulus (this condition serves to force participants to utilize the 1st retrocue and not simply rely on the 2nd retrocue for probe information). The probes will be identical to those from experiment 1. A second retrocue then appears (on half the trials, the same stimulus will be cued again), followed by a final delay and the probe.

9.Sub-study I. Testing the effects of TMS on connectivity between delay-active frontal and parietal regions with posterior visual regions involved in stimulus-specific storage. Participants will perform a delayed-recall task for visual motion and color (motion and color on separate blocks of trials). Each trial will begin with the presentation of an endogenous cue arrow (1 s), indicating the visual hemifield to be attended to during the trial. Following the cue, three sets of dots will be presented sequentially (500 ms each, 250 ms ISI) on each side of the screen, with either 1 or all 3 sets on each side moving/colored. Following a

delay period (2 s), participants will be required to recall the color or direction of motion of one of the stimuli from the attended side, indicated by a numeral representing the sequential position of the dot pattern to recall in the center of the screen. Participants will recall this direction/color by rotating (with a trackball) an indicate bar within a circular aperture/color wheel until it points towards the remembered color or direction. During the delay period (randomly 750ms-1250ms into) single pulse TMS will be delivered to one of three sites identified using fMRI localizer scans collected earlier: 1: Area MT+ (identified with a moving vs. static dot pattern localizer task), 2: interparietal sulcus (IPS) (identified from areas showing a parametric increase in activity during the delay period between loads one and three and 3: dorsolateral prefrontal cortex (dlPFC) (identified similarly to IPS).
Experimental Design: Single-pulse TMS, at 100 V/m as calculated by NBS, will be delivered once per trial during the delay period. There will be a minimum of 7.5 seconds between TMS pulses. Subjects will complete a total of 576 trials, for a total of 576 pulses delivered during the experiment.

10. Sub-study K. Oscillatory dynamics of near-threshold TMS-induced percepts. This study examines the neural dynamics associated with conscious perception of TMS-induced percepts called phosphenes. While recording EEG and finding near-threshold stimulation intensities whereby participants report experiencing phosphenes on roughly 50% of trials, we aim to exam the pre-stimulus EEG activity that is predictive of whether a participant experiences a phosphene on that trial or not. We also aim to examine the neural activity occurring after the TMS pulse that distinguishes trials where phosphenes were reported from those when they were not. Participants will first complete a structural MRI scan for later use in TMS targeting. Participants will then receive TMS to their primary visual cortex as well as posterior parietal cortex, where phosphenes have been reported in the past. For each stimulation site, and after each pulse is delivered, participants will respond verbally if a percept was present or not. The TMS stimulation intensity will be gradually increased until a threshold is found for each participant where 5 out of 10 stimulations result in a phosphene. Since a minority of the population do not see phosphenes, we will exclude participants who have not reported percepts after 100 stimulations at 90% of the maximum stimulator output. This threshold will be used for the remainder of the behavioral task. Participants will then be seated in front of a computer screen and, while recording EEG, will be asked to maintain fixation on a crosshair in the center of the black screen. TMS pulses will be delivered at pseudo-random intervals, followed by a 1 second black screen. Using a computer mouse, participants will then report on a sliding scale (1-100) their confidence that a percept was present.
Experimental Design: A total of 800 TMS pulses will be delivered: 400 at primary visual cortex and 400 at posterior parietal cortex, all using the intensity defined during the thresholding procedure. There will be between 3.5 to 6.5 seconds between the application of each TMS pulse. The MRI scan and TMS-EEG session will take place on different days.

11.Sub-study N. Examining the role of DLPFC in promoting visual-stimulus awareness and emotional regulation using TMS (MRI-guided). In a within-subjects design, following the delivery of TMS to either the dorsolateral prefrontal cortex (DLPFC) or a control region, postcentral gyrus (PoCG), behavioral tasks will be performed during an EEG session and will be similar to those approved in protocols HS-IRB #2011-0542 and SE-IRB # 2012-0100 (Lapate et al., 2014). Behavioral tasks will comprise two tasks: the emotional misattribution paradigm, and a visual awareness task. Briefly, in the emotional misattribution paradigm, participants will be shown valenced facial expressions, which will be followed by neutral stimuli (neutral faces, abstract images) shortly thereafter (1000-5000ms). Participants will then be asked to indicate with a button press their preference ratings for the novel neutral stimuli. EEG data will be continuously recorded. In addition, pupil diameter and skin conductance responses may be collected to obtain information about the magnitude of emotional change evoked throughout the session. Following this task, participants' visual awareness of the valenced facial expressions will be assessed using two 2-alternative forced choice paradigms (2AFC) where individuals will be asked to report on stimulus properties (e.g., face orientation; facial expression), as well as subjective visibility (i.e., clarity of the visual experience) using the Perceptual Awareness Scale (PAS). These 2 tasks combined will comprise no more than 288 trials and will take no longer than 40 minutes to complete, totaling a session (per TMS target; DLPFC and PoCG) of less than 1 hour. Participants will also be asked to complete questionnaires assessing their mood. We will pilot two previously approved TMS protocols (sub-studies A and G), offline theta-burst repetitive (tb) TMS, and online single pulse to determine which method is best suited for DLPFC inhibition in the context of this experiment. Both online and offline TMS modes of stimulation fall under the safe use guidelines of TMS that our lab has followed on all previous sub-studies (for TBS risk/benefit differences/similarities, see sub-studies A & G). In the session with single-pulse TMS to DLPFC vs. PoCG, the single TMS pulse will be delivered immediately prior to the presentation of the valenced facial expressions.

The **two aims** of this study are **(1)** to directly probe whether DLPFC plays a causal role in preventing emotional misattribution when individuals are aware of emotional stimuli and **(2)** to examine whether the hypothesized DLPFC role in preventing emotional misattribution is mediated via its effect on subjective visual awareness of the emotional stimuli. Conscious (e.g., visual) awareness of an emotional stimulus has been reported to modulate behavior following emotional processing, with greater emotional misattribution following unaware relative to aware emotional-stimulus processing, which is typically seen as valence-congruent shifts in evaluative ratings (e.g., likeability) of novel neutral stimuli (Li, Moallem, Paller, & Gottfried, 2007; Murphy & Zajonc, 1993; Rotteveel, de Groot, Geutskens, & Phaf, 2001). The neural bases of this effect have begun to be explored (Lapate et al, submitted) and are consistent with the role DLPFC is known to play in emotional regulation (Delgado, Nearing, Ledoux, & Phelps, 2008; Erk et al., 2010; Lee, Heller, van Reekum, Nelson, & Davidson, 2012) and

behavioral regulation (Figner et al., 2010; Hare, Camerer, & Rangel, 2009; Knoch, Schneider, Schunk, Hohmann, & Fehr, 2009; Steinbeis, Bernhardt, & Singer, 2012). Critically, DLPFC engagement during visual-stimulus processing is a neural correlate of subjective visual awareness (Lau & Passingham, 2006), i.e., being associated with the internal representation of the stimulus that facilitates conscious access to it. Accordingly, depression of DLPFC via tbTMS impairs subjective access to visual stimuli, namely, simple geometric shapes (Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010). Given the evidence for the role of DLPFC function for promoting subjective awareness of visual stimuli, and goal-oriented (rather than stimulus-driven) behavior, it is hypothesized that inhibitory TMS stimulation over DLPFC (vs. control area, PoCG) will produce increased emotional misattribution. Further, subjective awareness of the visual stimuli is postulated to be reduced via DLPFC inhibition and to function as a plausible mediator of the DLPFC inhibition effect on emotional misattribution. The current study aims to test these two hypotheses by inhibiting DLPFC via TMS as participants undergo the emotional misattribution and awareness tasks.

Experimental Design: *Theta-burst TMS (tbTMS)*

As in Study G, we propose to use a continuous TBS protocol that consists of 50 Hz trains of three TMS pulses repeated every 200 ms continuously over a period of 40 seconds (600 pulses total). Continuous TBS has been shown to depress activity in the stimulated brain region for up to 60 minutes following stimulation (Huang et al., 2005, 2009). The TBS procedure will be the same as in previously published studies (Huang et al., 2005, 2009; Lee and D'Esposito, 2012; Andoh and Zatorre, 2012; Morgan et al, 2013) and will follow the established safety guidelines (Rossi et al, 2009; Oberman et al, 2011). The risk of adverse events during TBS is comparable to or less than the other conventional high frequency repetitive TMS protocols (Rossi et al 2009, Oberman et al, 2011). *Single-pulse TMS* As in Study A, Single-pulse TMS, at 100 V/m as calculated by NBS, will be delivered once per trial, immediately prior to the presentation of the valenced facial expressions. There will be a minimum of 6 seconds between TMS pulses. When combining the emotional misattribution and awareness tasks for each PoCG and DLPFC sites, subjects will complete a total of 576 trials, for a maximum total of 576 pulses delivered during the experiment.

Questionnaires:

Subjects will fill out several well-validated questionnaires to evaluate mood and assess potential TMS- induced mood chances, which will be completed during their visits at the Waisman and HERI Laboratory. They will take approximately 15 minutes to complete, and will include the following measures:

1. Positive and Negative Affect Scales-State & -Trait (PANAS; Watson, Clark, & Tellegen, 1988)
2. The Implicit Positive and Negative Affect Test (IPANAT; Quirin et al., 2009)
3. Spielberger State Anxiety Inventory X-1 & Spielberger Trait Anxiety Inventory X-2 (STAIX; Martuza & Kalistrom, 1974)
4. The Toronto Alexithymia Scale (TAS; Parker et al., 2003)

5. The Mindfulness Attention Awareness Scale (by Davidson)
6. Inhibitory Control Scale from the Adult Temperament Questionnaire (Evans & Rothbart, 2007)
7. Emotion Regulation Questionnaire (Gross & John, 2003)

12.Sub-study P: Temporal Expectations as measured with EEG

This sub-study will build on the findings of sub-study K. Behavioral task will be completed while EEG is recorded from an EGI system 256 electrode cap. The task was about 1 hour, plus 1 hour of EEG setup. Subjects have to decide whether a briefly presented oriented grating is tilted to the left or the right and then rate their subjective visibility of that grating. On each trial, a color cue appears before the grating that indicated when the grating would appear relative to the cue. Some cues are predictive, in that the grating always appears after the same delay following the cue. Some cues are unpredictive, because they do not predict when the stimulus would appear. Subjects are instructed to use the cue to anticipate when the stimulus would appear. This is done while EEG data is recorded.

13.Sub-study Q: Speed of alpha oscillations and temporal resolution of perception measured with EEG

This sub-study addresses the question of whether there is a correlation between the speed of individuals' alpha oscillations (measured with EEG) and the temporal resolution of their perception. EEG data is recorded from a 60-channel cap connected to an Eximia 60-channel amplifier (Nextim, Helsinki, Finland) while subjects complete a two-flash fusion task. The task aims to determine the minimum time between two successive light flashes needed to perceive two, as opposed to one, distinct flashes. Subjects are seated 70 cm away from the monitor with a 100 Hz screen-refresh rate. Each trial begins with a central fixation cross (.98 degrees of visual angle) that reduces luminance to prepare subjects for the stimuli. The duration of the warning period is drawn from a uniform distribution between 1000 and 1500 ms. The fixation cross is present throughout the trial and the screen background is black. Grey disk stimuli are presented left or right of the fixation with equal probability and are always in the same location within a trial. Half of the trials are two-flash trials in which the first disk stimulus was present for 40 ms, followed by a blank screen of 10, 20, 30, 40 or 50 ms duration, followed by a 40 ms disk. The other half involves one-flash trials for which a single disk is presented. Subjects indicate whether they saw one or two flashes with a key press on a computer keyboard. The experiment takes 1.5 hours in total.

14. Sub-study R: Investigation of visual perception

In this experiment (lasting approximately 2 hours total), EEG and fMRI signal will be simultaneously recorded while subjects perform a visual detection task. A stimulus will be presented, and subjects will be asked whether it was a face or a

house; then, they will be asked how visible the stimulus was on a pseudo-continuous scale.

15.Sub-study L.1 Comparing the effects of single pulse TMS to attended and unattended items in short-term memory (MRI-guided).
In this sub-study subjects will be presented with two stimuli (a face, a word, or a patch of coherently dots moving in a random direction). The center of the screen is marked with a cross on which the subjects must keep their eyes throughout the trial. The stimuli are followed by a 5 second delay period and then a cue (arrows) indicating which item (top or bottom) is to be remembered for an upcoming memory probe. A single pulse of TMS is applied 2.5 seconds after the cue; the memory probe is presented 2 seconds after the TMS pulse. Then another cue is presented to indicate which item is to be remembered for a second memory probe presented after another 4.5-second delay. Subjects indicate with a button press whether or not the memory probe matches the cued item. The difference in the TMS evoked response on the EEG during the delay period when subjects are remembering attended (cued) versus unattended (uncued) items in short-term memory is of interest. Therefore, in each of the three EEG sessions, TMS is targeted to an area identified as important for representing each category of stimulus (face, word, motion) during a short-term memory delay period, providing observations of the TMS evoked response when the targeted category is in each of three states: attended, unattended, or absent on that trial. Single pulse TMS will be delivered at 90-110 V/m 2.5 seconds after the cue on each trial. Single pulse TMS delivered at 90-110 V/m will be applied during the delay period to a face selective, word selective, or motion selective region of interest. There will be a 3 second interval between all trials. Subjects will perform eight blocks (consisting of 24 trials) per stimulation site. (Total of 192 trials.)

16.Sub-study L.2. Comparing behavioral effects of single pulse TMS on reactivation of representations for unattended memory items.
Sub-study L.2 will replicate the procedures of L.1., except that on half of the trials the uncued item will be tested (25% of total trials for the first probe and 25% of total trials for the second probe). For this sub-study, subjects will have only the anatomical fMRI and no task will be completed in the scanner. No EEG will be recorded during this task. Single pulse TMS will be delivered at 90-110 V/m after the cue on each trial. Single pulse TMS delivered at 90-110 V/m will be applied during the delay period to the Precuneus (a portion of the superior parietal lobule). There will be a 2 second interval between all trials. Subjects will perform ten blocks (consisting of 36 trials) per stimulation site. (Total of 360 trials.) Half of the total trials (180) will probe the uncued item. Half of these ‘catch’ trials will occur on the first and the other on the second probe. Probe 1 ‘catch’ trials will end after the first probe.

Sub-study J. Behavioral and EEG effects of Area MT Stimulation on Transparent Motion Memory and Perception. This sub-study will test the hypothesis that cortical area MT in humans is crucial for representing multiple directions of simultaneously moving stimuli both during the stimulus presentation period and during the Working Memory (WM) delay period that follows the visual stimuli. Human subjects will first view visual stimuli composed of random dots moving simultaneously in two directions, which gives rise to the percept of two superimposed surfaces moving transparently in different directions. The angle of separation between these moving dot surfaces is systematically varied from 0-60 degrees in order to probe the nature of the percept. This stimulus aperture will be presented in the left visual hemi-field at an eccentricity of 5.5 degrees away from the center of fixation, corresponding to the site used in the MRI localizer task for identifying area MT in each subject. After a 1 second delay period following this initial presentation (the “sample”), the subject will be cued as to which set of moving dots they should respond to. The subjects will then be presented with a circle, at the center of which is the mouse cursor (“probe”). They will make an outwardly radial mouse movement towards the outer edge of the circle in the direction they perceived the cued stimulus to have been traveling (“response”). When the probe is presented following a delay, information about motion needs to be stored in visual WM for subsequent output as a mouse movement. We will deliver repetitive Transcranial Magnetic Stimulation (rTMS) to cortical area MT of human subjects either during the visual stimulation period or the WM delay period, with simultaneous recoding of EEG. In addition to the blocks of trials performed with MT stimulation, we will perform a smaller number of trial blocks with area S1 stimulation as a control. We will measure behavioral performance in terms of the error between the response and sample directions and compare these measures under both TMS-on and TMS-off conditions. Many of the results obtained here will help guide the study design for future experiments probing this same question in monkeys as part of a collaboration with Xin Huang. Repetitive TMS trains at 10 Hz delivered at 110% of the resting motor threshold intensity, will be applied for 1.0 sec either during the delay period or during the stimulus presentation to area MT/V5 plus to a postcentral gyrus control site (S1). There will be a 2 second interval between all trials, meaning subjects will not experience successive trains of rTMS with an interval shorter than 6 seconds. Subjects will perform 7 blocks (consisting of 30 trials) at the MT/V5 stimulation site and 3 blocks of 30 trials at the postcentral gyrus control stimulation site. This gives a total of 300 trials, 200 featuring repetitive TMS (for each block, 1/3 of trials have rTMS during the delay period, 1/3 have rTMS duing the stimulus presentation period and 1/3 of trials have no rTMS; all are randomly distributed throughout a block). The total number of pulses that will be delivered in this experiment is 2000. Repetitive TMS will be delivered in 1.0 sec-long trains of 10 Hz at 110% of the resting motor threshold intensity, at either the beginning of the delay period or at the start of stimulus presentation. There will be a 2 second interval between all trials, meaning that the shortest possible time between successive trains of

rTMS is 6 seconds (corresponding to a “delay period stimulation” trial being followed by a “stimulus period stimulation” trial).

Sub-study S: Decoding memory for visual motion.

This sub-study attempts to decode a subject’s memory for visual motion. The study duration is one fMRI scan which takes approximately 2.75 hours. During the scan, the subject performs two tasks. For the first task, the subject fixates on a central dot that changes between blue and red. While the central dot is blue, the subject is instructed to hold down the button, and when the central dot is red, the subject is instructed to release the button. During this task, there is a patch of dots in the subject’s peripheral vision. The dots alternate between moving or remaining stationary. The subject is instructed to pay attention to the patch of dots without averting his/her gaze away from the central colored dot. After three rounds of this task, the second task begins. For the second task, the subject fixates on a central white cross that brightens just before the trial starts. Shortly after, the dots appear to be moving in one direction. The goal of the task is for the subject to remember the direction of the moving dots by mentally visualizing the moving dots even after they are no longer on the screen. A few seconds later, a wheel with a central radial spoke appears on the screen. To indicate the direction of motion of the moving dots from the subject’s memory, the subject aligns the spoke with the direction the dots were traveling and click the left trackball button. After the response, the central cross changes color to indicate the accuracy of the response.