Project Narrative

Internal distractions are a well-recognized impediment to high-level performance on a wide variety of activities. The goal of this project is to understand the factors that influence the self-regulation of internal distraction, as well as the underlying neural mechanisms that govern this regulation and our ability to learn how to better self-regulate with practice. This knowledge will be used to further our understanding of basic principles underlying self-regulation, and to help design future interventions to improve abilities to regulate the impact of distractions in diverse populations.

Project Summary

A major obstacle to high-level performance on a wide variety of goal-directed activities is interference by distractions. This interference can arise from the external environment, in the form of distracting sounds, images and smells, as well as from the internal milieu, as unwanted, intrusive thoughts. In concordance with recent theories on mind-wandering, we propose that all individuals have a tendency to automatically succumb to internal thoughts that are irrelevant to their ongoing goals, and that this is influenced by cognitive and emotional states and their surrounding environment. The degree to which they are capable of self-regulation of these internal distractions mediates the impact of this interference on goal-directed behavior. The objectives of the proposed research project are to evaluate the factors that impact self-regulation of internal distraction and the neural correlates that account for differences in self-regulation abilities across individuals and age groups, as well as the ability to learn to better self-regulate distraction. Specifically, we will explore how regulation of mind-wandering is influenced by task orientation (internal vs. external), and whether the presence of external distraction influences the regulation of internal distraction. We will evaluate if there are differences in executive function and neural networks that explain differences in these self-regulation abilities. Lastly, we assess the neural mechanisms by which self-regulation of internal distraction can be modified via practice. To accomplish these goals, we designed novel cognitive paradigms to evaluate the self-regulation of internal distraction, and the influence of the described factors, in both healthy younger and older adults. Next, using functional MRI, we will study the neural correlates of internal distraction regulation, as well as a failure to adequately suppress distractions. Finally, we utilize a novel distraction-training program, inspired by meditation practices and plasticity-based cognitive training, to study the neural basis of learning to self-regulate internal distraction. In addition, an extensive battery of cognitive tasks and real-life activity measures will be administered to evaluate correlates of these neural and experimentally-assessed distraction measures. We anticipate that the unique methodological approach and experimental design will significantly advance the limited work in this important area of self-regulation.

Mechanisms of Self-Regulation of Internal Distraction

Specific Aims

A major obstacle to achieving high-level performance on a wide variety of activities is interference by both external and internal distraction. Goal-directed activities themselves can either be oriented towards the external environment (e.g., visual and auditory attention and memory encoding), or involve an internal orientation (e.g., planning for the future, remembering past events, and maintaining items in short-term memory). During any of these activities, interference can arise from the external world in the guise of distracting sounds, images, smells, etc; or internally in the form of distracting, unwanted, intrusive thoughts (i.e., mind-wandering). Self-regulation involves mechanisms of suppressing these distractions in order to maintain high-level performance on goal-directed tasks.

Our laboratory has extensively characterized neural correlates of external interference and its impact on many types of behavior, including those with external and internal orientations. In this proposal, we will investigate behavioral, cognitive and neural aspects of the self-regulation of internal distraction. Specifically, we will explore how regulation of mind-wandering is influenced by task orientation, how the presence of external distractors influences the self-regulation of internal distraction, if there are differences in executive function and neural networks that explain differences in self-regulation abilities, and the mechanisms by which self-regulation of internal distraction can be modified via practice and training. To accomplish this, we propose the following aims:

Specific Aim 1: Understand how self-regulation of internal distraction is influenced by the orientation of goals (internal vs. external), external environment (presence or absence of noise), and individual characteristics (including age and executive function).

Experiment 1: Healthy younger adults (ages 18 – 35) will engage in a behavioral experiment to explore the frequency of mind-wandering and cognitive performance while engaged in two tasks: (1) an externally-oriented visual monitoring task; (2) an internally-oriented, working memory maintenance task. During each of these tasks, a subset of trials will include varying levels of auditory distraction to probe how external interference impacts internal distractor suppression. These same participants will also undergo extensive cognitive testing and behavioral surveys of personality and life activities to assess the relationship between self-regulation of internal distraction and other aspects of behavior and cognitive abilities.

Experiment 2: We will compare data from the younger adults in Expt. 1 to healthy older adults (ages 60-80) on the same behavioral tasks in order to assess whether older individuals have alterations in internal distractor suppression, and if this is related to established deficits in external distractor suppression in this population.

Specific Aim 2: Understand the neural correlates of self-regulation of internal distraction.

Experiment 3: Neural measures associated with mind-wandering and the suppression of internal distractors will be assessed using fMRI (both regional activity and network connectivity), while younger adults engage in the previously described tasks. We will specifically focus on the ‘default network’ and ‘frontoparietal attention network’, as well as functional connectivity between these networks and early sensory-motor cortices.

Specific Aim 3: Understand the neural basis of learning to better regulate internal distraction.

Experiment 4: We developed a novel, meditation-influenced and neuroplasticity-based cognitive training program focused on improving self-regulation of attention, metacognitive awareness and suppression of internal distraction. Younger adults studied with fMRI in Expt 3, will enage in a training program and in fMRI post-training using the behavioral tasks described above to explore the neural mechanisms involved in learning to self-regulate internal distraction. Moreover, cognitive testing pre-post training will probe the transfer of this learning to other cognitive abilities.

We anticipate that the unique methodological/analytical approach and experimental design of this project will have a major impact on the study of self-regulation. Understanding basic mechanisms of self-regulation of internal distraction, and the plasticity of such self-regulatory abilities with practice is a major neuroscience challenge. Beyond addressing important basic science goals, studies of this nature are amongst the most likely to rapidly translate to therapeutic interventions directed at a range of mental illnesses. In summary, the completion of this project will result in a more sophisticated understanding of the neural basis of self-regulation of internal distraction and set the stage for more effective interventions.

RESEARCH STRATEGY

(a) SIGNIFICANCE

Self-Regulation of Internal Distraction. Self-regulation can be broadly defined as the process of engaging in goal-directed behavior while suppressing distractions that are a source of interference to accomplishing these goals (1-3). Such distraction may arise from irrelevant stimuli in the external environment (4-6), from the internal milieu as intrusive thoughts, emotions and urges (7-14), or as a complex interaction between these two sources (1; 15). Failure to adequately control or regulate the impact of external and internal distraction can lead to significant impairment in cognition (4-6; 16-19), social conduct (20), and affect regulation (1; 15; 21). Pathological failure to regulate this interference likely plays an important role in a range of mental illnesses (22; 23), including ADHD (both distractibility and hyperactive behaviors) (24), PTSD (intrusive recollections triggered by external cues) (25; 26), Major Depressive Disorder (ruminations, impairments in cognition and attention), Obsessive Compulsive Disorder (uncontrollable anxieties/obsessions, compulsive behaviors), and Substance Dependence Disorders (uncontrollable cravings, contextual triggers for relapse) (27). For all these reasons, understanding how we control, suppress and regulate both internal and external interference is fundamental to understanding self-regulation processes (28).

To understand the behavioral cost and neural correlates of the impact of external distraction on goal-directed behaviors, our laboratory has pioneered a multi-methodological approach, coupling fMRI and EEG with novel cognitive paradigms and analytical techniques. Our approach has led to new conclusions regarding spatial and temporal mechanisms of top-down modulation in the setting of external interference, the neural networks that underlie them and the changes that occur in this system with normal aging (4; 5; 16-19; 29-39). In a series of studies, we have shown that in the presence of external distraction, early modulation of stimulus processing minimizes distraction cost (4; 29; 30) and resistance to the negative impact of distraction on memory involves maintaining functional connectivity between the prefrontal cortex (PFC) and visual cortical regions (31-33).

In this proposal, we will extend this approach to study self-regulation of internal distraction. Prior research on internal interference has focused on studies of “mind-wandering”. Ecological studies of mind-wandering show that this phenomenon occurs between 30 – 40% of our waking time (21; 40; 41), during almost every behavior and task that has been monitored (21; 40), and with demonstrable costs in performance (42) and emotional health (21). There is evidence that mind-wandering reflects both state-dependent changes in cognitive status (varying inversely with both task difficulty and arousal) (14; 43), and trait-level differences in executive function (11) (varying inversely with working memory capacity) (9; 10). fMRI neuro-imaging has begun to demonstrate some of the neural correlates of these phenomena. During mind-wandering there is an increase in neural activity in the default network that is dependent on the nature of the ongoing activity (7; 12; 44) (a network of brain areas that are more active during non-task oriented behaviors (23; 44)), and the predilection of participants to mind-wander in general correlates with increased activity in this network during cognitive tasks (7; 9). More recently, studies have demonstrated activity in frontal executive circuits during mind-wandering (7), although it is unclear as yet whether this activity is involved in the regulation of mind-wandering, or is active as a result of task demands implicit to mind-wandering itself.

In this proposal, we explore behavioral and neural correlates associated with self-regulation of mind-wandering, and specifically test the hypothesis that regulation of both internal and external distractions relies on shared or overlapping neural circuits. Using a novel task design and functional neuroimaging, we will study for the first time the effect of external distractions on internal distraction regulation, in particular evaluating whether external distractors engage neural systems and suppression mechanisms that result in automatic suppression of internal distractors; or, alternatively, whether external interference taxes distractor suppression mechanisms and therefore impairs the ability to regulate internal distractions. Using behavioral questionnaires, we will further explore whether differences in internal distraction regulation is related to real-world behavioral differences (for example, the propensity to seek out noisy vs. quiet work environments).

Orientation of Behavior and Distraction Regulation. Similar to how interference can arise from either internal or external sources, goal-directed behavior itself can be viewed as either internally- or externally-oriented. Behaviors that are “externally-oriented” are those that depend on the presence of external stimuli e.g., paying attention to external visual or auditory stimuli, reading, or memory encoding); behaviors that are internally-oriented are those that occur in the absence of any external stimuli: e.g. planning, memory retrieval, calculation, interoception/awareness of internal states and mental imagery. Working memory includes both an externally-oriented phase (memory encoding), and an internally-oriented one (maintenance period, during which individuals no longer rely on external stimuli). Many studies from our lab have shown that external distraction interacts with both externally-oriented tasks, such as memory encoding and attention (34; 17; 19; 35; 36); as well as internally-oriented tasks, such as memory recall (5). To our knowledge, no studies have evaluated how task orientation interacts with the regulation of internal distraction. For example, it is unknown whether it is more difficult to regulate internal distracting thoughts when one is engaged in an internal monitoring task vs. an external monitoring task. In this proposal, we plan to study internal distraction suppression during both internally- and externally-oriented tasks to understand how different cognitive orientations impact distraction regulation.

Distractor Suppression in Older Adults. In addition to studying a healthy population of younger adults, we will explore whether individuals with known deficits in external distractor suppression demonstrate similar deficits in the self-regulation of internal distraction. We have previously shown that older individuals experience deficits in the suppression of externally-presented distracting information (34), that these deficits occur at early visual processing stages (17; 18; 37; 35) and that this is mediated by a failure to maintain functional connectivity between prefrontal and visual cortices (34). In contrast to this deficit in external distraction suppression, older adults have been shown to exhibit fewer internal distractions during certain tasks compared to young adults (45). This potential discrepancy between deficits in internal and external distractor suppression in older adults clearly warrants exploration. The current proposal aims to better characterize the ability to self-regulate internal distractions during healthy aging and also evaluate the effects that external distraction has on the self-regulation of internal distracting stimuli in healthy older adults (ages 60 – 80). Using cognitive testing and behavioral questionnaires, we will further explore whether there is a relationship between these two aspects of suppression.

(b) INNOVATION

Novel Training Program to Explore Self-Regulation of Distraction. In our laboratory, we have demonstrated that the impact of external distraction on working memory performance decreases with task practice in both younger and older adults (34; 16). This behavioral evidence reveals that we can learn with practice to minimize the impact of external distraction. To our knowledge, there have been no studies to assess whether self-regulation of internal distractions is a skill similarly amenable to training improvements. Assessing this would be informative both from a clinical standpoint, but also from the perspective of understanding neural and behavioral mechanisms of self-regulation. In contrast to the lack of evidence in the literature on improving internal distraction regulation with training, meditation training demonstrates a wealth of cognitive changes (46-58), suggesting the possibility that it results in improvements in internal distraction regulation. Meditation training has been subdivided into at least three categories: "focused attention training", "open-awareness" training, and "compassion meditation" training (47; 48; 59). In practice, most meditation combines many, if not all of these training categories, and so assaying the effects specific to different regimens has proven elusive (60). Moreover, the impact of selection bias on meditation effects in cross-sectional studies involving experienced mediators has complicated many of these studies. Nonetheless, meditation training has been shown to improve perceptual discrimination (61; 62), sustained attention (47; 48; 46; 53; 55; 57; 56) and other aspects of self-regulation (such as behavioral and emotional) (58), with concurrent modification of anatomical and functional neural circuitry associated with these cognitive functions (46; 55; 57; 49; 54; 63-66). In addition to cognitive improvements, meditation is associated with a wide range of important physiological effects (61), including stress reduction (67-70), changes in immune function and hormone levels (48; 71), and improvements in markers of cellular aging (72).

In this proposal, we have developed a novel, computer-based, internal distraction training program designed to integrate aspects of meditation training (attention to breath, monitoring quality of attention), while incorporating features that underlie the plasticity-based approach to training: repetitiveness, quantifiable goals, feedback and adaptivity of the training program. This novel "East meets West" approach to studying internal distraction regulation training is not intended to replace the many physiological benefits that meditation engenders, including stress reduction, body awareness, and compassion. But rather, by focusing on a constrained aspect of meditation (focused attention and awareness of internal distractions), we reduce variabilities involved in standard meditation practice, thus allowing us to study the effects of directed training on self-regulation of internal distraction.

(c) APPROACH

<u>Experimental Overview</u>. The proposed project is a series of experiments that will be organized into two phases. In the first phase, 50 younger adults (18 – 35 years of age) and 50 older adults (60 – 80 years of age) will be recruited to undergo cognitive and behavioral testing on a novel behavioral paradigm, as well as cognitive tests of executive function. Following these behavioral experiments, all participants will undergo a battery of questionnaires designed to assess real-life abilities to regulate both internal and external distractions, the extent of multi-media exposure, personality, mood and study/work habits (e.g., ability and/or preference to work in distracting environments). In the second phase, the younger adults will undergo a neuroimaging study with fMRI to evaluate neural correlates of the self-regulation of internal distraction. Following this, the effects of a novel computer-based, meditation-inspired training program will be evaluated in a longitudinal study of the younger adults. In this phase, the 50 younger adults studied above will be randomly enrolled into one of two groups: a “no-contact” control group and an “internal distraction regulation” training group, with 25 participants in each group. Participants in both training groups will then engage in 20 hours of training distributed over the course of 2 months (averaging 2.5 hours/week). Following this, participants will return to the lab for post-training cognitive testing and fMRI. We recently conducted a study on the neural basis of visual discrimination learning using a training program in older adults (38). That study serves as a critical milestone for the proposed project as it demonstrates our ability to perform a study in the proposed manner and in the time window proposed in the grant. Based on our experience with cognitive training, a maximal attrition rate of 10% is predicted, which will result in at least 20 individuals in each study group with complete datasets. The sample size tables of Lauter (73) indicate that an alpha=0.05 level test of the difference in five dimensional outcomes for 20 participants would have power 0.8 to detect an effect size of 0.5 (73). Stevens (74) notes that this effect size would be classified as "large" according to Cohen's scheme (75).

- **Participants**. 50 younger (18-35 years of age) and 50 older (60-80 years of age) adults will be recruited to participate in the behavioral experiment in Phase 1. Younger participants will be recruited only if they are able to commit to both behavioral testing and the longitudinal fMRI - training study of Phase 2.

- **Location**. Gazzaley lab for behavioral testing and the UCSF Neuroscience Imaging Center for the neuroimaging. Training sessions will be conducted both in the laboratory (eight 1 hour sessions conducted weekly to ensure standardization) combined with an additional 12 hours of training at home.

- **Screening**. All participants will undergo initial screening for study inclusion, ensuring that none have a history of neurological disease or current psychiatric illness, or have a MMSE score lower than 27. Medication information will be collected; exclusions will be for cholinesterase inhibitors, memantine and psychotropic medication. Vision testing with a Snellen chart will be performed and acuity differences corrected to 20/40 or better, and participants will be screened for hearing difficulties using single tone frequencies between the range of 500 – 3000 Hz, with exclusion for significant loss at multiple frequencies.

- **Cognitive assessment**. A cognitive testing battery will be used to assess relationships between standardized measures of attention, working memory and distractibility and the novel behavioral task we are using in this study. These tests will include assessment of: a) *Attention*: Test of Variables of Attention (76); Continuous Performance Task (13), (b) *Attentional Capacity*: Multiple Object Tracking (77); c) *Working Memory Capacity (78)*: Change Detection Task (79); d) *Distractibility*: Auditory Consonant Trigrams (80), Stroop Test (81), Filter Task (13), 2- & 3-back task (13); and e) *Emotion Distraction Regulation*: emotional distraction/working memory task (15). In addition, there will be a battery of lifestyle, personality and mood questionnaires, including those used in the ACTIVE study *(143)* and media multitasking study *(16)*).

- **Behavioral Study of Internal Distraction.** This study was designed to probe two primary questions. 1) Is the regulation of internal distraction differentially impacted by engagement in internally- vs. externally-oriented goals. 2) Is the self-regulation of internal distraction influenced by the presence of external distraction. To probe these questions, we designed a novel cognitive paradigm to measure the degree of internal distraction (i.e., mind-wandering) during either internally-oriented or externally-oriented tasks, and in the presence or absence of external distraction.

<u>Experimental Design:</u> The experiment will be divided into a series of 12 blocks, with each block consisting of twenty 30-32.5 sec trials (thus, lasting between 10-10.8 min long). Six blocks will involve an externally-oriented task (visual target discrimination, described below) and six will involve an internally-oriented task (working memory maintenance, described below). Four of the six blocks in each task will contain auditory distractors (recorded conversations, with two blocks presented at low-volume and two blocks presented at high volume, as described below). Blocks will be presented in a pseudo-randomized order across participants. Task performance will be assessed, as well as the presence of internal distraction measured using well-validated, experience sampling techniques adapted from previous studies of mind-wandering (7; 8; 10; 14; 43; 82), which have been shown to correlate with other laboratory measures and real-world assays of mind-wandering (40-

42). In total, there will be 40 trials for each of the 6 different conditions (external task and internal tasks, each with no distraction, low-volume and high volume distractions) to assay cognitive performance on the task and the frequency of mind-wandering, calculated as % trials in which a mind-wandering event occurred over total number of trials for that behavioral condition. The task timing presented below is based on our view of the relevant literature and experience with cognitive testing; it will be evaluated with extensive pilot testing and adjusted as necessary to assure the presence of reasonable frequency of mind-wandering events.

- External task: Visual Target Discrimination. Prior to the experiment, participants will be instructed that when they are in an external task block they will make a button press to all target signs, and withhold responses to non-target signs. At the start of each trial, participants will be informed of a colored shape that will appear as the target sign (e.g., green circle) on a computer screen (2.5 sec cueing period). A hit on a target sign, indicated by the fixation cross turning green, occurs if a response is made within a pre-defined time window. This time window is established prior to the experiment using a staircase thresholding procedure that individually determines the response window duration that results in discrimination task performance of 80% accuracy. 10% of the signs are targets, 45% are contingent, non-target signs (share the color dimension) and 45% are non-contingent, non-target signs (share no feature). These stimuli will be presented for 20 sec, followed by a cue at the end of the trial to report the presence of mind-wandering at any time during the duration of that trail (2.5 sec response period). The next trial begins in 5 sec (total trial length= 30 sec). In addition to recording mind-wandering events, performance data will include hits, misses, correct rejections, false positives and response time for the sign discrimination task.

- 2) Internal task: Working Memory Maintenance. Prior to the experiment, participants will be informed that when they are in an internal task block they will be presented an "encoding" set of signs to maintain in mind during each trial. Encoding signs (from 1 to 8 colored shapes identical to those used in the external task) appear on a black background 3 degrees above a central fixation cross at the start of every trial. Participants will have 2.5 sec to encode these signs. This set of signs will be followed by a working memory maintenance period of 20 sec, during which time participants will be tasked to rehearse and keep in memory the encoded signs. After which they will be asked to first report the presence of an encoded sign in a "test" set (2.5 sec response period), and then report the presence of mind-wandering during the maintenance period (2.5 sec response period). The next trial begins in 5 sec (total trial length= 32.5 sec). Thus, parallel to the external task, the presence of mind wandering over the 20 sec period of task engagement will be assessed, as well as task performance (% correct on memory task). In order to match difficulty level with the external task, the number of memoranda to maintain in working memory will be pre-determined for each individual prior to the experiment using a staircase thresholding procedure that individually optimizes WM maintenance at 80% accuracy.

- 3) External Distraction. Both of the tasks described above will be performed in blocks conducted either in silence, or in the presence of an auditory distractor (presented only during the 20 sec of target discrimination or working memory maintenance, respectively). To explore how the presence of external distraction impacts regulation of internal distraction, we chose to mimic a "real-world" example of external distraction. Thus, recorded restaurant background conversations will be delivered to the participants via sound cancellation headphones as the auditory distraction (83). These stimuli have been used in our lab in a recent study of auditory distraction (Wais et. al, submitted). These auditory distractions will be played continuously during the 20 sec period of interest at two different volumes to modulate difficulty; a low volume (starting at 10dB, thresholded for each participant to 10dB greater than 'just audible') to serve as a weaker distractor, and a higher volume (20dB greater than low-volume threshold level, not to exceed 60 dB) to serve as a stronger distractor. Thus, we will be able to assess the impact of external distraction on the internal distractibility.

- 4) Age-related Effects. Following completion of the study on younger adults, we will enroll 50 older participants (ages 60-80) to assess whether the ability to self-regulate internal distraction under these conditions changes with aging. As stated above, the goal of this study is two-fold: to evaluate the regulation of internal distractions in older adults; and to assess the relationships between internal and external distractions in a population with known deficits in external distraction suppression.

- **Neural Assessment**. To assess neural mechanisms of internal distractibility, fMRI data will be collected while younger participants are engaged in the experimental tasks described above, modified slightly to support an fMRI design. All visual stimuli will be viewed via a coil-mounted mirror on an LCD screen mounted at the rear of the scanner bore, and auditory stimuli will be delivered using noise-cancelling headphones. Manual responses will be recorded via an MR–compatible joystick with a response button. In the fMRI version, there will be a total of eight 10-minute blocks: two blocks of each task (working memory and visual target detection) with auditory distractions (using the “loud” noise distractor described above), and two blocks of each task without extra auditory distractions (participants will have a noise-cancelling headphone set to minimize scanner noise). Blocks will be presented in a pseudo-randomized order across participants. For the fMRI task, in addition to collecting data on mind-wandering at the end of every trial using experience sampling methodologies as explained above, participants will be instructed to press a button each time they become aware that a mind-wandering event is occurring (7). In this way, we will generate both event-specific neural data of mind-wandering events, and data that will be collapsed across trials in which mind-wandering occurred to be compared to mind-wandering free trials. As in all fMRI studies by our lab, in addition to the experimental tasks there will be a series of independent localizer tasks, which enable the localization of visual and motor regions of interest (ROIs) that are selectively associated with perceptual and motoric aspects of the tasks. Also, passive view tasks will be used to control for bottom-up perceptual activity. In addition, there will be an 8-minute scan at rest to evaluate baseline functional connectivity.

- **Training Program**. The training program was designed by integrating meditation-based practices and lessons from plasticity-based cognitive training approaches. Training will be split between the lab (8 hour-long sessions, to allow for monitoring and standardization of task practice) and home (24 half-hour long sessions) distributed over the course of two months. Participants will begin by starting a computer program in a quiet location, with headphones on and eyes closed, and attend to the sensation of the breath in their nostrils. In addition to having a focus of attention (breath sensation), participants will be asked to monitor the quality of their attention and to be particularly aware of any internal distracting thoughts that may arise. When these thoughts do occur, participants will be tasked to be aware of the distraction, disengage from it, and shift their attention back to the sensation of their breath. They will be instructed to choose a quiet room relatively free of external auditory distraction for this training. The training described above will be integrated with plasticity-based, cognitive-training methods, including quantifiable goals, feedback and adaptivity. Training will begin with short trials in which participants will be instructed to maintain attention on their breath (starting with 15 sec trials). At the end of each trial, participants will be cued by an auditory signal to open their eyes and report with a button-press whether their attention remained on their breath throughout the trial, or if their attention was diverted at any time by internal distracting thoughts (i.e., mind-wandering). If the trial was successful (i.e., maintained attention to breath) the duration of the next trial will be increased by 2 seconds, and if unsuccessful, the duration of the next trial will be decreased by 2 seconds. By adaptively modifying the duration of the trials based on this criterion, the ability to regulate internal distraction will be selectively targeted. In addition, participants will be given regular feedback on their distractibility level throughout each session and at the end and beginning of each session (reflected as the trial duration, or the ‘level’ they achieved). Standardization of training across individuals will be accomplished via the 8 hour-long training sessions in the lab. Following the training period, participants will undergo the cognitive battery and the fMRI experiment that was used during the pre-training evaluation.

- **Hypotheses and analytical approach**. We propose, in concordance with recent theories on mind-wandering (11), that all individuals have a tendency to automatically succumb to internal thoughts that are irrelevant to their ongoing goals, and this is influenced by cognitive and emotional states and their surrounding environment. The degree to which they are capable of self-regulation of these internal distractions mediates the impact of this interference on goal-directed behaviors. Specifically, individuals with an optimal ability to self-regulate will exhibit minimal mind-wandering, and when this does occur it will have only a mild impact on objective measures of performance. We will evaluate the factors that impact self-regulation of internal distraction and the neural correlates that explain differences in self-regulation abilities across individuals and age groups, as well as explore the neural mechanisms of learning to better self-regulate.

o <u>Factors that impact the self-regulation of internal distraction</u>. The following questions will be addressed using the behavioral data collected in phase 1: How does the orientation of cognitive goals (internal vs. external) influence the regulation of internal distraction? How does the presence of external distractions (at both low and high levels) impact cognitive performance and internal distractor suppression? To what degree do older adults, a population with established deficits in external distractor suppression, have deficiencies in internal distractor suppression? Performance testing and experience sampling measures will be used to calculate the frequency of internal distraction when engaged in both internally and externally-oriented attention tasks, and the impact of varying degrees of external distraction on the frequency of internal distraction and task performance. These measures will be compared within-group using 2X2 ANOVAs with factors of Task (external, internal) X External Distraction (present, absent) followed by post-hoc t tests, and across-group in a 3-way ANOVA with age as the across-group factor. It is predicted that internal distraction will be greater with internal tasks, and that external distraction will improve the self-regulation of internal distraction (at least for a subset of individuals, perhaps explaining why some seek out coffee shops to study). Regression analyses will be performed to capitalize on individual differences and assess the relationship between internal distraction (as well as the influence of the studied factors on distraction) and executive function and life activities.

Neural correlates of self-regulation of internal distraction. Over the last eight years, we developed and extensively published results using a novel methodological/analytical approach to study neural mechanisms of top-down modulation. Focusing on the pre-training fMRI data, this approach will be applied to this project in the following manner to yield new insights on the neural basis of internal distraciton: 1) We will assess BOLD activity in stimulus-selective sensory cortices during each of the tasks. These regions of interest will be identified by contrasting activity in a series of independent localizer tasks. 2) Next, we apply functional connectivity analysis to fMRI data using a method we developed to identify network regions that serve as potential control sources of top-down modulatory signals (beta series correlation analysis (31; 33). 3) We then perform contrasts between conditions, and also capitalize on individual variability and performance fluctuations across trials to investigate neural-behavioral relationships. This is accomplished by regression analyses of univariate and functional connectivity data with performance. Data will be assessed both for internal distraction events (as identified as a 4-sec period preceding an indication by participants of mind-wandering), and comparisons between whole trials without mind-wandering (successful self-regulation of internal distraction) and whole trials with mind-wandering (failed self-regulation of internal distraction). Comparisons will be performed of neural activity/networks associated with internal distraction during both the internal task and external task, and with and without the presence of additional auditory distraction.

By studying neural differences associated with the regulation of internal distractions, both in the presence or absence of external distractions, we aim to clarify the role of executive networks (notably, frontoparietal network) in this regulation process. Based on a review of the literature and our previous work, we hypothesize that a failure to suppress internal distractions is due to deficient interactions between frontoparietal and default-mode networks, as well as early sensory areas. We predict that external distraction will reduce the presence of internal distraction by engagement of a common suppression mechanism, which will extend our previous work on external suppression of distraction. As in previous studies from our lab, capitalizing on individual differences across participants using whole-brain regression analyses will strengthen conclusions based on contrasts. Specifically, by comparing mind-wandering present trials across participants with varying degrees of mind-wandering, we will evaluate how differences in network connectivity correlates with an overall tendency to mind-wander. Regression analyses will also be performed for mind-wandering absent trials (i.e., successful self-regulation). The conclusions will be further extended by evaluating how neural measures of internal distraction relate to independently obtained measures of distractibility, executive function and life activities.

- Mechanisms of learning to resolve internal distraction. The following behavioral questions will be addressed to evaluate the overall impact of internal-distraction training: Does visual target discrimination, working memory and self-regulation of internal distraction improve following a 20-hour distractor suppression training program, and are there cross-over effects, such that internal distraction training results in an improved ability to suppress external distractions? These questions will be addressed using ANOVAs with factors of Time × Group to evaluate pre- and post-training lab assessments. Next, post-training fMRI will allow us to assess changes in neural networks that correlate with behavioral improvements, such as enhancements in functional connectivity between the default network and frontoparietal network both at rest and during tasks, as well as increased functional connectivity between frontoparietal regions and early sensory areas.

As described, to assess training-mediated cognitive and neural effects, within-group ANOVAs and multivariate regressions will be conducted for pre- and post- training data. Data will also be evaluated by splitting participants into performance subgroups. Additionally, training gain will be calculated as: TG = (post-training – post-control) – (pre-training – pre-control), and the *effect size*: ES = TG/ intra-participant SD.

- **Summary.** Upon the completion of this project, we will have addressed the following unresolved questions regarding self-regulation of internal distractions: 1) Understand how internal distraction (mind-wandering) is influenced by the orientation of goal-directed behavior and the presence of external distraction. 2) Understand the neural mechanisms that underlie these influences. 3) Evaluate individual differences in these factors and how they change with age. 4) Evaluate the influence of practice/training on internal distraction regulation. We expect the unique approach of this project will have a major impact on our understanding of self-regulation processes at multiple levels of analysis, and serve as a foundation for the development of future interventions targeting improved self-regulation.

References

1. Beauregard M, Levesque J, Bourgouin P. Neural Correlates of Conscious Self-Regulation of Emotion. J. Neurosci. 2001 Sep;21(18):165RC.

2. Rueda MR, Posner MI, Rothbart MK. The Development of Executive Attention: Contributions to the Emergence of Self-Regulation. Developmental Neuropsychology 2005;28(2):573.

3. POSNER MI, ROTHBART MK, SHEESE BE, TANG Y. The anterior cingulate gyrus and the mechanism of self-regulation. Cognitive, Affective, & Behavioral Neuroscience 2007 Dec;7(4):391-395.

4. Clapp WC, Rubens MT, Gazzaley A. Mechanisms of Working Memory Disruption by External Interference. Cerebral Cortex 2010 Apr;20(4):859 -872.

5. Wais PE, Rubens MT, Boccanfuso J, Gazzaley A. Neural Mechanisms Underlying the Impact of Visual Distraction on Retrieval of Long-Term Memory. Journal of Neuroscience 2010;30(25):8541.

6. Clapp WC, Gazzaley A. Distinct mechanisms for the impact of distraction and interruption on working memory in aging. Neurobiology of aging 2010 Feb;(Epub)

7. Christoff K, Gordon AM, Smallwood J, Smith R, Schooler JW. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proceedings of the National Academy of Sciences 2009;106(21):8719.

8. Kane MJ, Brown LH, McVay JC, Silvia PJ, Myin-Germeys I, Kwapil TR. For Whom the Mind Wanders, and When. Psychological Science 2007 Jul;18(7):614 -621.

9. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering Minds: The Default Network and Stimulus-Independent Thought. Science 2007;315(5810):393-395.

10. McVay JC, Kane MJ. Conducting the Train of Thought: Working Memory Capacity, Goal Neglect, and Mind Wandering in an Executive-Control Task. J Exp Psychol Learn Mem Cogn 2009 Jan;35(1):196-204.

11. McVay JC, Kane MJ. Does mind wandering reflect executive function or executive failure? Comment on Smallwood and Schooler (2006) and Watkins (2008). Psychological bulletin 2010;136(2):10.

12. Preminger S, Harmelech T, Malach R. Stimulus-free thoughts induce differential activation in the human default network. NeuroImage 2011; 54(2); 1692-702.

13. Smilek D, Carriere JSA, Cheyne JA. Out of Mind, Out of Sight: Eye Blinking as Indicator and Embodiment of Mind Wandering. Psychological Science 2010;21(6):786-789.

14. Braboszcz C, Delorme A. Lost in thoughts: Neural markers of low alertness during mind wandering [Internet]. NeuroImage 2010; (Epub)

15. Dolcos F, McCarthy G. Brain systems mediating cognitive interference by emotional distraction. Journal of Neuroscience 2006;26(7):2072.

16. Berry AS, Zanto TP, Rutman AM, Clapp WC, Gazzaley A. Practice-related improvement in working memory is modulated by changes in processing external interference. Journal of neurophysiology 2009;102(3):1779.

17. Clapp WC, Gazzaley A. Neural basis for the negative impact of multitasking on working memory in older adults. (in press).

18. Gazzaley A, Cooney JW, Rissman J, D'Esposito M. Top-down suppression deficit underlies working memory impairment in normal aging. Nature neuroscience 2005 Oct;8(10):1298–300.

19. Zanto TP, Gazzaley A. Neural suppression of irrelevant information underlies optimal working memory performance. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009 Mar;29(10):3059–66.

20. Aron AR, Poldrack RA. The Cognitive Neuroscience of Response Inhibition: Relevance for Genetic Research in Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry 2005;57(11):1285 - 1292.

21. Killingsworth MA, Gilbert DT. A Wandering Mind Is an Unhappy Mind. Science 2010;330(6006):932.

22. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. Neuroscience & Biobehavioral Reviews 2009;33(3):279–296.

23. Buckner RL, Andrews-Hanna JR, Schacter DL. The Brain's Default Network: Anatomy, Function, and Relevance to Disease. Annals of the New York Academy of Sciences 2008;1124(1):1-38.

24. Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, Schweitzer JB. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Research 2009 Jun;1273:114-128.

25. Nemeroff CB, Bremner JD, Foa EB, Mayberg HS, North CS, Stein MB. Posttraumatic Stress Disorder: A State-of-the-Science Review. Focus 2009 Apr;7(2):254-273.

26. Yehuda R, LeDoux J. Response Variation following Trauma: A Translational Neuroscience Approach to Understanding PTSD. Neuron 2007 Oct;56(1):19-32.

27. Sayette MA, Schooler JW, Reichle ED. Out for a Smoke. Psychological Science 2010 Jan;21(1):26 -30.

28. Posner MI, Rothbart MK. Attention, self-regulation and consciousness. Philos Trans R Soc Lond B Biol Sci 1998 Nov;353(1377):1915-1927.

29. Rutman AM, Clapp WC, Chadick JZ, Gazzaley A. Early Top–Down Control of Visual Processing Predicts Working Memory Performance. Journal of cognitive neuroscience 2010;22(6):1224–1234.

30. Gazzaley A, Cooney JW, McEvoy K, Knight RT, D'Esposito M. Top-down enhancement and suppression of the magnitude and speed of neural activity. Journal of cognitive neuroscience 2005 Mar;17(3):507–17.

31. Gazzaley A, Rissman J, D'Esposito M. Functional connectivity during working memory maintenance. Cognitive, affective & behavioral neuroscience 2004 Dec;4(4):580–99.

32. Gazzaley A, Rissman J, Cooney J, Rutman A, Seibert T, Clapp W, D'Esposito M. Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. Cerebral cortex 2007 Sep;17 Suppl 1:i125–35.

33. Rissman J, Gazzaley A, D'Esposito M. Measuring functional connectivity during distinct stages of a cognitive task. NeuroImage 2004 Oct;23(2):752–63.

34. Clapp WC, Gazzaley A. Distinct mechanisms for the impact of distraction and interruption on working memory in aging [Internet]. Neurobiology of Aging 2010; (Epub)

35. Zanto TP, Toy B, Gazzaley A. Delays in neural processing during working memory encoding in normal aging. Neuropsychologia 2010 Jan;48(1):13–25.

36. Zanto TP, Hennigan K, Ostberg M, Clapp WC, Gazzaley A. Predictive knowledge of stimulus relevance

does not influence top-down suppression of irrelevant information in older adults. Cortex; a journal devoted to the study of the nervous system and behavior 2010 Apr;46(4):564–74.

37. Gazzaley A, Clapp W, Kelley J, McEvoy K, Knight RT, D'Esposito M. Age-related top-down suppression deficit in the early stages of cortical visual memory processing. Proceedings of the National Academy of Sciences of the United States of America 2008 Sep;105(35):13122–6.

38. Berry AS, Zanto TP, Clapp WC, Hardy JL, Delahunt PB, Mahncke HW, Gazzaley A. The Influence of Perceptual Training on Working Memory in Older Adults. PLoS ONE 2010 Jul;5(7):e11537.

39. Bollinger J, Rubens MT, Zanto TP, Gazzaley A. Expectation-driven changes in cortical functional connectivity influence working memory and long-term memory performance. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010 Oct;30(43):14399–410.

40. McVay JC, Kane MJ, Kwapil TR. Tracking the train of thought from the laboratory into everyday life: An experience-sampling study of mind wandering across controlled and ecological contexts. Psychonomic Bulletin & Review 2009 Oct;16(5):857-863.

41. Smilek D, Carriere JS, Cheyne JA. Failures of sustained attention in life, lab, and brain: Ecological validity of the SART. Neuropsychologia 2010 Jul;48(9):2564-2570.

42. Smallwood J, Fishman DJ, Schooler JW. Counting the cost of an absent mind: Mind wandering as an underrecognized influence on educational performance. Psychonomic bulletin & review 2007;14(2):230.

43. Smallwood J, Schooler JW. The restless mind. Psychological Bulletin 2006;132(6):946.

44. Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL. Evidence for the Default Network's Role in Spontaneous Cognition. Journal of Neurophysiology 2010; Jul; 104(1): 322-35.

45. Giambra LM. Task-Unrelated-Thought Frequency as a Function of Age: A Laboratory Study. Psychology and Aging 1989 Jun;4(2):136-143.

46. Pagnoni G, Cekic M. Age effects on gray matter volume and attentional performance in Zen meditation. Neurobiology of aging 2007;28(10):1623–1627.

47. Lutz A, Slagter H, Dunne J, Davidson R. Attention regulation and monitoring in meditation. Trends in Cognitive Sciences 2008;12(4):163-169.

48. Tang YY, Posner MI. Attention training and attention state training. Trends in cognitive sciences 2009;13(5):222–227.

49. Hölzel BK, Ott U, Hempel H, Hackl A, Wolf K, Stark R, Vaitl D. Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. Neuroscience Letters 2007 Jun;421(1):16-21.

50. Jha AP, Stanley EA, Kiyonaga A, Wong L, Gelfand L. Examining the protective effects of mindfulness training on working memory capacity and affective experience. Emotion 2010;10(1):54–64.

51. MacLean KA, Ferrer E, Aichele SR, Bridwell DA, Zanesco AP, Jacobs TL, King BG, Rosenberg EL, Sahdra BK, Shaver PR, Wallace BA, Mangun GR, Saron CD. Intensive Meditation Training Improves Perceptual Discrimination and Sustained Attention. Psychological Science 2010;21(6):829-839.

52. Van Dam NT, Earleywine M, Borders A. Measuring mindfulness? An Item Response Theory analysis of the Mindful Attention Awareness Scale. Personality and Individual Differences 2010 Nov;49(7):805-810.

53. Valentine ER, Sweet PLG. Meditation and attention: A comparison of the effects of concentrative and

mindfulness meditation on sustained attention. Mental Health, Religion & Culture 1999;2(1):59.

54. Slagter HA, Lutz A, Greischar LL, Francis AD, Nieuwenhuis S, Davis JM, Davidson RJ. Mental training affects distribution of limited brain resources. PLoS Biol 2007;5(6):e138.

55. Lutz A, Slagter HA, Rawlings NB, Francis AD, Greischar LL, Davidson RJ. Mental Training Enhances Attentional Stability: Neural and Behavioral Evidence. J. Neurosci. 2009 Oct;29(42):13418-13427.

56. Jha AP, Krompinger J, Baime MJ. Mindfulness training modifies subsystems of attention. Cognitive, Affective, & Behavioral Neuroscience 2007;7(2):109.

57. Brefczynski-Lewis JA, Lutz A, Schaefer HS, Levinson DB, Davidson RJ. Neural correlates of attentional expertise in long-term meditation practitioners. Proceedings of the National Academy of Sciences 2007 Jul;104(27):11483 -11488.

58. Tang YY, Ma Y, Wang J, Fan Y, Feng S, Lu Q, Yu Q, Sui D, Rothbart MK, Fan M, others. Short-term meditation training improves attention and self-regulation. Proceedings of the National Academy of Sciences 2007;104(43):17152.

59. Raffone A, Srinivasan N. The exploration of meditation in the neuroscience of attention and consciousness. Cogn Process 2009;11(1):1-7.

60. Cahn BR, Polich J. Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychological Bulletin 2006;132(2):180-211.

61. Dooley C. The Impact of Meditative Practices on Physiology and Neurology: A Review of the Literature. (Vol 4. 2009): pp1-59.

62. MacLean KA, Ferrer E, Aichele SR, Bridwell DA, Zanesco AP, Jacobs TL, King BG, Rosenberg EL, Sahdra BK, Shaver PR, Wallace BA, Mangun GR, Saron CD. Intensive Meditation Training Improves Perceptual Discrimination and Sustained Attention. Psychological Science 2010;21(6):829-839.

63. Jaeggi SM, Berman MG, Jonides J Training Attentional Processes. Trends Cogn Sci 2009; 13(5):191-2.

64. Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, McGarvey M, Quinn BT, Dusek JA, Benson H, Rauch SL, Moore CI, Fischl B. Meditation experience is associated with increased cortical thickness. Neuroreport 2005 Nov;16(17):1893-1897.

65. Luders E, Toga AW, Lepore N, Gaser C. The underlying anatomical correlates of long-term meditation: Larger hippocampal and frontal volumes of gray matter. NeuroImage 2009;45(3):672–678.

66. Slagter HA, Lutz A, Greischar LL, Nieuwenhuis S, Davidson RJ. Theta phase synchrony and conscious target perception: Impact of intensive mental training. Journal of cognitive neuroscience 2009;21(8):1536–1549.

67. Speca M, Carlson LE, Goodey E, Angen M. A Randomized, Wait-List Controlled Clinical Trial: The Effect of a Mindfulness Meditation-Based Stress Reduction Program on Mood and Symptoms of Stress in Cancer Outpatients. Psychosom Med 2000 Sep;62(5):613-622.

68. Kaplan S. Meditation, restoration, and the management of mental fatigue. Environment and Behavior 2001;33(4):480.

69. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits: A meta-analysis. Journal of Psychosomatic Research 2004 Jul;57(1):35-43.

70. Astin JA. Stress Reduction through Mindf ulness Meditation. Psychother Psychosom 1997;66(2):97-106.

71. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. Psychoneuroendocrinology 2004 May;29(4):448-474.

72. Epel E, Daubenmier J, Moskowitz JT, Folkman S, Blackburn E. Can Meditation Slow Rate of Cellular Aging? Cognitive Stress, Mindfulness, and Telomeres. Annals of the New York Academy of Sciences 2009;1172(1):34-53.

73. Lauter J. Sample Size Requirements for the T-square Test of MANOVA (Tables for One-way Classification). Biometrical Journal 1978;20:389–406.

74. Stevens J. Applied multivariate statistics for the social sciences. Hillsdale, NJ: Routledge; 2002.

75. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Routledge; 1988.

76. Greenberg LM, Waldman ID. Developmental normative data on the test of variables of attention (T.O.V.A.). Journal of child psychology and psychiatry, and allied disciplines 1993 Sep;34(6):1019–30.

77. Green C, Bavelier D. Enumeration versus multiple object tracking: the case of action video game players. Cognition 2006 Aug;101(1):217-245.

78. Kane MJ, Engle RW. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. J Exp Psychol Gen 2003 Mar;132(1):47-70.

79. Fukuda K, Vogel EK. Human Variation in Overriding Attentional Capture. J. Neurosci. 2009 Jul;29(27):8726-8733.

80. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. Clinical Neuropsychologist. 1987;1(2):139–152.

81. Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, Weiner MW, Chui HC. Longitudinal MRI and Cognitive Change in Healthy Elderly. Neuropsychology 2007 Jul;21(4):412-418.

82. Davidson RJ. Empirical explorations of mindfulness: Conceptual and methodological conundrums. Emotion 2010;10(1):8–11.

83. Kerlin JR, Shahin AJ, Miller LM. Attentional Gain Control of Ongoing Cortical Speech Representations in a "Cocktail Party". J. Neurosci. 2010 Jan;30(2):620-628.