

## **Suggested Parameters for Common Magnetic Resonance Imaging (MRI) Scans**

When possible, it is preferable for ME/CFS neuroimaging studies to use common scanning protocols. The use of common protocols increases the compatibility of data with other laboratories and studies, allowing ME/CFS data to be compared and contrasted with other diseases and healthy controls. To-date, the most implemented common parameters come from the NIH Human Connectome Project (HCP). The HCP provides suggested hardware, software, scan parameters, and other study elements to ensure data acquired is most compatible with those from other MRI research centers. Suggested protocols are provided for T1-weighted structural, T2-weighted structural, resting state fMRI, task-evoked fMRI, and diffusion-weighted imaging. Studies that follow the HCP protocol guidance are considered to be “HCP-like”. The full reference manual and protocol guidance can be found at:

[http://humanconnectome.org/storage/app/media/documentation/data\\_release/Q1\\_Release\\_Appendix\\_1.pdf](http://humanconnectome.org/storage/app/media/documentation/data_release/Q1_Release_Appendix_1.pdf)

Brief parameters for 3 Tesla scans can be found at the below page:

<http://protocols.humanconnectome.org/HCP/3T/imaging-protocols.html>

Protocol details for functional tasks (cognitive, motor, and emotional processing) can be found at:

<http://protocols.humanconnectome.org/HCP/3T/task-fMRI-protocol-details.html>

In addition, the following fMRI tasks have been used at least in 2 studies specific to the investigation of fatigue in ME/CFS populations:

### **Auditory and Visual Information processing/working memory tasks:**

#### **mPasat**

##### **Lange et al., 1998; Cook et al., 2007**

Description of experimental and control tasks excerpted from publications: Finger tapping task: Participants were instructed to focus on a crosshair (i.e., 3" × 3" white + on a black background) at the center of the screen and to open and close their right hand, bringing their four fingers in contact with their thumb, at the same rate as the crosshair once it began to flash (120 min- 1). Participants were instructed not to make a fist, but instead to repeatedly bring the tips of their four fingers in contact with the tip of their thumb. Movement stopped when the crosshair stopped flashing. The task consisted of four 30-second on-periods preceded and followed by 30-second off-periods for a total of 4 min and 30 s. A second finger tapping task, identical to the first, was presented as the last task at the end of the functional imaging scanning session to determine the influence of accumulated mental fatigue on motor responses.

Simple auditory monitoring task:

Participants were instructed to listen to a series of numbers ranging from one to ten and to press the left mouse button when they heard the number seven. Each number was presented for 1500 ms and separated by 500 ms. The task consisted of four 30-second on-periods that were preceded and followed by 30-second off-periods for a total of 4 min and 30 s. Twenty events were presented during each 30-second on-period. Of these, seven events (35%) were correct targets (i.e., the number 7). Task performance was quantified as the percentage of correct responses and the reaction time of the correct responses.

Difficult task involving attention, working memory and executive function processes: A modified version of the PASAT was used to induce feelings of mental fatigue during fMRI scanning. The PASAT requires participants to attend to and encode auditory information and retrieve it from the working memory system (Tombaugh, 2006). For the primary task, participants listened to a series of numbers ranging

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from one to nine. They were instructed to continually and silently add the first number to the second, the second number to the third and so on and to press the button whenever two consecutive numbers summed to the number ten. Each number was presented for 1500 ms and was separated by 500 ms. The task consisted of three 3-minute on-periods and four 30 s off-periods for a total of 11 min. One hundred and twenty events were presented during each three-minute on-period. Of these, forty-two (35%) were correct targets (i.e., two numbers summing '10'). As a secondary task, participants were instructed that, in addition to listening to the numbers presented as part of the PASAT, they were to visually focus on a set of three boxes that contained rapidly (every 500 ms) and randomly changing numbers. The rate at which the visual numbers were presented was intentionally made too rapid for any arithmetic and was purely intended to distract and interfere with the primary auditory task, thereby increasing the complexity and attentional demands of the task and inducing greater mental fatigue. Participants were instructed that no action was required on their part for the distracting numbers. Thus, the participants were instructed to listen to the numbers presented through the headphones and perform the serial addition task on these auditory numbers, while simultaneously focusing on the numbers scrolling on the screen. In order to ensure participant compliance to the task, we reiterated the task instructions prior to each 3-minute on-period and stressed the importance of keeping their eyes open. Furthermore, we instructed them that we would be able to view their performance through the projection mirror and that we would remind them to open their eyes should they accidentally close them. Ratings of mental fatigue were obtained immediately prior to and immediately following each 3-minute block of the task. Task performance was defined as the percentage of correct responses and the reaction time to the correct responses.

### **Boissoneault et al., 2016**

(Different version from mPASAT used above)

The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) is a well-validated cognitive task of auditory information processing speed and flexibility, as well as calculation ability (Tagliazucchi & Laufs, 2015). It has good psychometric properties including high levels of internal consistency and test-retest reliability (Tombaugh, 2006). Critically, the PASAT has been successfully used as a cognitive challenge in functional neuroimaging studies of fatigue (Cook et al., 2007). To ensure standardization of presentation, auditory stimuli consisting of single- or double-digit numbers were computer-generated and presented in pseudorandom order at two different interstimulus intervals (ISIs). During the first 3 min of the PASAT, stimuli were presented with an ISI of 3 s. During the subsequent 9 min, the ISI was decreased to 2 s. Subjects added each number to the preceding one and determined whether they summed to 13 (target value). Across the duration of the PASAT, 35% of number combinations added to 13. Performance feedback (i.e. correct versus incorrect) was provided after each subject response. Subjects indicated their response (yes or no) using a keypad. They continuously rated their overall fatigue on an electronic VAS from 0 ('no fatigue') to 100 ('most intense fatigue imaginable') for the duration of the scan using a scroll wheel placed in their other hand. The scale was visible during the entire scan on a large computer screen, and subjects were instructed to adjust their ratings if fatigue changed. The PASAT and VAS were implemented and presented using PsychoPy (Peirce, 2007, 2009) running on a Dell Latitude laptop (Dell Inc., Round Rock, TX, USA).

### **Parametric verbal and visual n-back tasks:**

#### **Caseras et al., 2006**

A verbal version of the n-back originally described by Braver et al. (13) was used. In a block design, three levels of difficulty (1-back, 2-back, and 3-back) and one control condition (0-back) were included.

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Participants were presented with a series of capital letters on a projection screen (which they saw through a mirror above their head) and were required to press a button whenever the letter presented was the same as that presented *n* trials previously (1-, 2-, or 3-back). During the control condition, participants were required to press the button whenever they saw the letter "X." All blocks consisted of a pseudorandom sequence of 21 letters presented for 1 second each and separated by an interstimulus interval of 1 second. Three blocks of each condition were presented, totaling 12 blocks in the following order: 1-back/2-back/0-back/3-back/2-back/0-back/1-back/3-back/2-back/3-back/0-back/1-back. The task had a total duration of 9 minutes.

A computer automatically recorded the participants' performance (accuracy and reaction time to target) during the task. All participants received a training session before scanning to ensure that they understood the task.

### **Rayhan RU et al., 2013**

Prior to both fMRI scans, subjects completed N-back practice sessions on a computer. Blocks of 9 randomized letters (A, B, C, D) were presented. Subjects were given instructions to respond by pressing a button for the same letter ("0-Back") or the one seen 2 letters previously ("2-Back"). Blocks for 0-back then 2-back tasks were presented for 5 cycles. A total score of 35 letters correct were possible during the 2-back working memory cognitive paradigm.

### **Ishii et al., 2013**

Used two-back task trials to induce the fatigue sensation and metronome sounds as the conditioned stimuli. During the two-back task trials, one of four letters was presented on a display of a personal computer every 3s and the participants had to judge whether the letter presented on the display at the moment was the same as the one that had appeared two presentations before. If it was, they were to press the right button with their right middle finger; if it was not, they were to press the left button with their right index finger. They were instructed to perform the task trials as quickly and as correctly as possible, and had to engage in two-back task trials for 60 min.