The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network

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In this protocol we describe how to perform the Multi-Source Interference Task (MSIT), a validated functional magnetic resonance imaging (fMRI) task that reliably and robustly activates the cingulo-frontal-parietal cognitive/attention network (CFP network) within individual subjects. The MSIT can be used to (i) identify the cognitive/attention network in normal volunteers and (ii) test its integrity in people with neuropsychiatric disorders. It is simple to perform, can be completed in less than 15 min and is not language specific, making it appropriate for children, adults and the elderly. Since its validation, over 100 adults have performed the task. The MSIT produces a robust and temporally stable reaction time interference effect (range 200–350 ms), and single runs of the MSIT have produced CFP network activation in approximately 95% of tested subjects. The robust, reliable and temporally stable neuroimaging and performance data make the MSIT a useful task with which to study normal human cognition and psychiatric pathophysiology.

INTRODUCTION

The dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC) and superior portions of parietal cortex combine to form part of a cingulo-frontal-parietal cognitive/attention network (CFP network)[1–5]. This brain network plays critical roles in attention and cognitive processing, but group-averaging techniques have generally been required to obtain significant activation of these brain regions in functional neuroimaging studies—a fact that limits progress. For example, while the Counting Stroop task has been useful in studying groups of healthy volunteers and patients[6], it has not been robust enough to produce brain activation in single subjects. Although such group-averaged tasks contribute greatly to our understanding of normal human information processing, pathophysiology and drug effects, they are not effective for use in clinical functional imaging contexts since they cannot be used to distinguish a patient from a healthy subject and/or other diagnostic groups. The MSIT was designed to address these needs.

In developing the MSIT as a task to be used for assessing the functional integrity of daMCC and DLPFC in neuropsychiatric disorders[7], we attempted to make it conform as closely as possible to the characteristics of a hypothesized ideal functional neuroimaging-based diagnostic test. Specifically, we strove to ensure that it possessed the following characteristics: (i) It must produce reliable and robust activation of the cortical region(s) of interest (ROI) within healthy individuals. (ii) It should be hypothesis driven (i.e., pre-existing evidence should support a mechanism explaining why the task would be expected to recruit the ROI. (iii) It should include collection of concomitant imaging and performance data (reaction times and accuracy). (iv) Testing procedures must be standardized. (v) The task instructions should be easy to learn and retain so that the task can be performed by subjects with impaired cognition (e.g., schizophrenia) and by subjects across a wide age range (to enable developmental studies in children and studies of elderly subjects). (vi) It should be of short duration, as children and elderly subjects generally cannot tolerate protracted testing. (vii) It should not be language specific (to facilitate cross-cultural studies). (viii) Performance data should vary within a relatively narrow range in healthy volunteers. (ix) Imaging and performance data should be related. (x) Imaging and performance data should show temporal stability (i.e., it should display sufficient test-retest reliability to permit longitudinal and treatment studies). (xi) Imaging and performance data should be sensitive to changes with successful treatment. (xii) Results should be disorder specific.

Seeking first to use existing tasks to study the attention network in attention-deficit hyperactivity disorder (ADHD) and schizophrenia, we did pilot work using cognitive interference tasks (in which the processing of one stimulus feature impedes the simultaneous processing of a second stimulus attribute). These would include Stroop and Stroop-like tasks[8–20], Eriksen Flanker-type tasks[21–23] and Simon effect task variants[18]. While full descriptions of these cognitive interference tasks from which the MSIT was derived are beyond the scope of this protocol, brief descriptions are given here. The essence of the prototypical cognitive interference task, the Color Stroop[9,24], is that subjects take longer to name the color of the ink that color-words are written in when the ink color and word are incongruent (e.g., the word 'red' written in blue ink) than when they do match ('blue' written in blue ink) or when the word is a non-color word ('house' written in blue ink). In the Eriksen Flanker Task[25] subjects take longer to identify a centrally located target letter (and make more errors) when the target letter is flanked by incongruent distractor letters (e.g., DDTDD) than when it is flanked by the same letter (e.g.,

TTTTT). The Simon Effect[26] denotes the cognitive interference produced by spatial incongruence between the target and response (e.g., given a two-button response pad, it takes longer for subjects to respond using the left button when the target appears on the right (and vice versa) than when the stimulus and response positions correspond). Indeed, these tasks have reliably activated the CFP network in group-averaged functional neuroimaging studies. This is not surprising, as such tasks place high demands on target detection, response selection and performance-monitoring circuits. However, none was robust enough to reliably and significantly activate the CFP network within single subjects. By combining multiple dimensions of cognitive interference (i.e., Stroop[24], Eriksen[25] and Simon[26]) with decision-making and other factors known to activate daMCC (target detection, novelty detection, error detection, response selection, stimulus/response competition and task difficulty)[27] all within a single stimulus trial, the MSIT (see **Fig. 1**) maximally taxes the CFP network, making it possible to reliably activate the CFP network within individuals.

Although the MSIT was developed primarily as a clinical functional neuroimaging test, its robust and stable behavioral and imaging effects also make it a powerful task for studying normal cognition and drug effects and for longitudinal studies. The MSIT has already been used to study normal volunteers[7,28] and patients with schizophrenia[29], and is currently being used in studies of ADHD pathophysiology, methylphenidate, atomoxetine and placebo, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), depression, aging and Tourette's; we are also using it in combined fMRI and intracranial recording studies. It has produced reliable and robust fMRI activation in approximately 95% of over 100 individuals and has generally supplanted the Counting Stroop in ongoing studies of cognition (but see ref. 6 for special cases in which the Counting Stroop is useful and preferable).

The main focus of attention of the MSIT's design was to develop a task that would maximally activate daMCC and the rest of the CFP network. Increasing attention, however, has recently been paid to understanding task-independent deactivation of 'affective circuitry' during cognitive task performance. More specifically, reciprocal responses have been repeatedly observed in daMCC and pregenual anterior cingulate cortex (pACC). That is, complex cognitive tasks increase daMCC activity and decrease pACC activity, whereas tasks involving emotion conversely produce decreased daMCC activity and increased pACC activity[1,30–34]. McKiernan and colleagues[35] reported that as cognitive task difficulty increased, the magnitude of task-independent deactivations of pACC also increased. In keeping with these findings, the MSIT's high difficulty and potent ability to activate the cognitive/attention CFP network also make it a potent deactivator of 'affective' brain regions in single subjects (including pACC, amygdala and posterior cingulate cortex). Thus, the MSIT might be used to functionally localize and test these affective areas in individuals and groups.

The MSIT protocol presented here is the recommended format to follow for block-formatted fMRI, SPECT or PET studies. However, it can easily be modified for use with event-related fMRI, ERPs, MEG or for simple offline behavioral studies. The MSIT is appropriate for use with subjects age 4 or 5 years and above (for very young children or elderly adults who may not respond via button press as quickly as typical adults, the rate of presentation (interstimulus interval) may be adjusted—in these specialized cases additional pilot testing may be needed to optimize the interstimulus interval). The MSIT's instructions can be translated into nearly any language, and should be presented in the subject's primary language.

The MSIT can be used to study healthy volunteers, control subjects, or subjects with neuropsychiatric disorders as appropriate to study goals. In all cases, documentation should be made of a history of neurological, major medical, or psychiatric disorder, medication status or serious head injury.

It should be noted that, based on our pilot data and early experience with the task, two minor changes were made to the MSIT since its original report[7]. First, the distractors were changed from the letter 'X' in the original to zero '0' in the revised version. Second, the targets and distractors are all presented the same size in the revised version (in the original version, distractors were always smaller than the target in the control trials and could be larger or smaller than the target in the interference trials). Preliminary experience showed that these changes have had no appreciable effect on either performance or imaging measures, and the changes have been instituted to facilitate task instructions and improve consistency of task presentation characteristics.

Formal testing: functional MRI scanning techniques and data analysis

As detailed above, the MSIT was designed to be an fMRI task, and the following portion of the protocol details the block-formatted parameters used. However, the MSIT can and has been easily be converted to an event-related format for use with event-related fMRI, ERPs, MEG, intracranial recordings or for simple offline behavioral performance (reaction time (RT)/accuracy).

Whether displayed on a computer screen (for offline studies, PET, MEG, ERPs) or projected for use during fMRI, individual sets of numbers should be easily read without strain but should not take up a large proportion of the visual field. Generally accepted guidelines would be to display individual numbers that subtend approximately 1° of visual angle vertically and 3° horizontally, and to group them together at the screen center without extra spacing.

Issues for studies of clinical populations

The MSIT possesses many of the qualities deemed desirable in a functional neuroimaging-based diagnostic test. (i) It reliably and robustly activates daMCC within individuals. (ii) Mechanistically, it is hypothesis driven. (iii) It permits collection of concomitant imaging and performance data. (iv) Testing procedures are standardized. (v) The task instructions are easy to learn and retain so that the task can be performed by subjects with impaired cognition and by subjects across a wide age spectrum. (vi) It can be completed in a short amount of time. (vii) It is not language specific, which can facilitate cross-cultural studies (i.e., at least across those cultures that use Arabic numerals). (viii) Performance data varied within a relatively narrow range. (ix) Imaging and performance data were related (i.e., increased RT was associated with higher fMRI signal). (x) Imaging and performance data showed temporal stability. Thus, it appears that the MSIT can be a useful task in studies of neuropsychiatric patients and normal volunteers. Of course, although we stress the value of the individual study, group-averaged MSIT data can also be used with the advantages of greater power, fewer subjects and higher confidence.

Although the MSIT shows promise as a cognitive task and potentially as a task that can assist with diagnosis of neuropsychiatric disorders, a vast amount of information about task characteristics remains to be explored. As larger numbers of subjects are studied, a greater understanding of the effects of many factors on performance and imaging results will be attained. For example, task format (block versus event-related), individual subject characteristics (age, intelligence, education, handedness, medication effects, disease presence/absence, affective state), practice effects and scanner strength can all potentially influence results and will need to be better characterized via future studies to improve task utility. Similarly, although the development of the MSIT was hypothesis driven, based upon the presumed single unit qualities of daMCC[7,27], future studies will help refine our understanding of the mechanisms by which the various components of the cingulo-fronto-parietal network operate. Our hope is that presentation of this revised version of the MSIT will assist other groups in implementing the task in a standardized way, thus facilitating the building of an MSIT database and comparisons of results among laboratories.

Conclusions

The MSIT produces reliable and robust activation of daMCC and the rest of the cingulo-fronto-parietal attention network in individuals and this closely matches the group-averaged data. Coupled with the reliable and robust performance data, the MSIT displays many of the characteristics desired in a neuroimaging-based diagnostic test. As such, it can be expected to serve as a useful fMRI probe in searching for the neural substrates of various neuropsychiatric disorders such as attention deficit disorder, schizophrenia, obsessive-compulsive disorder, posttraumatic stress disorder and depression. Future studies could also use task manipulations to further elucidate mechanisms of attention, response selection and cognition.

MATERIALS

- Human subjects: Handedness is not crucial, but should be assessed at least by subject self-report (preferably documented by the Edinburgh Handedness Inventory[36] or other inventory). ▲ **CRITICAL** Subjects need to have normal or corrected-to-normal vision.

! CAUTION The study protocol must be approved for use by the appropriate Human Subjects Committee or Institutional Review Board, and informed consent must be obtained following the established institutional and national guidelines.

EQUIPMENT

- MRI scanner. Functional MRI equipment and scanning techniques can appropriately vary. Our fMRI studies have been performed on Siemens 3.0 tesla (and 1.5 T) Allegra high-speed echo-planar imaging devices and a GE Signa 1.5 T magnet (modified by Advanced NMR Systems) using a quadrature head coil.
- Magnet-compatible button-press response device (see EQUIPMENT SETUP)
- Padded scanner couch
- Foam ear plugs
- Head stabilizer (e.g., foam padding within a head coil, or a plastic bite bar molded to each subject's dentition)
- Stimulus generator. Stimuli can be generated via any number of software/hardware configurations. Our stimuli have been created/displayed using MacStim 2.5–3.0 (Dave Darby, WhiteAnt Occasional Publishing, http://www.brainmapping.org/WhiteAnt) and Presentation (Neurobehavioral Systems, http://www.neurobs.com), but any suitable stimulus presentation software/hardware combination that can smoothly display stimuli and record responses (and RT to millisecond accuracy) can be used (see EQUIPMENT SETUP).

EQUIPMENT SETUP

For the button-press response device, only three buttons are needed, although a four-button setup is typical, in which case the fourth button is ignored. Buttons should be sized and spaced such that they approximate a typical keyboard input device (i.e., subjects should be able to comfortably place the index, middle and ring fingers of the right hand on the keypad).

Whether displayed on a computer screen (for offline studies, PET, MEG, ERPs) or if projected for use during fMRI, individual sets of numbers should be easily read without strain but should not take up a large proportion of the visual field. Generally accepted guidelines would be to display individual numbers that subtend approximately 1° of the visual angle vertically and 3° horizontally, and to group them together at screen center without extra spacing.

PROCEDURE

Subjects

1| Obtain informed consent from subjects and document handedness and vision.

Psychophysical procedures

2| Give subjects the button-press device and instruct them that the keypad buttons represent one, two and three from left to right.

3| Tell subjects to use the index, middle and ring fingers of the right hand to respond. Depending on individual study parameters and goals, subjects can theoretically use either hand to respond, but unless there is a special case in question, the right hand is preferable, as it provides in most cases a more natural digit (number) to digit (finger) mapping, which eliminates the potential for Simon effect[26] interference of spatial incongruity between answer and response selection.

▲ **CRITICAL STEP** Responses are to be recorded by pressing the selected button. An MSIT variant[28] that instructed subjects to use a very different response method predictably found atypical RT results (i.e., in that study, rather than recording responses by pressing one of three buttons located immediately beneath the three fingers, trials began with subjects holding down a central button, and RT was measured as the time it took to release this central button and to initiate a response toward one of three response buttons that were located 14 cm away—precluding meaningful comparison to standardized existing data).

4| Instruct subjects that sets of three numbers (1, 2, 3 or 0) will appear in the center of the screen every few seconds, and that one number will always be different from the other two (matching distractor) numbers.

5| Instruct subjects to report, via button-press, the identity of the number that is different from the other two numbers. Inform subjects that during some (control) trials, the target number (1, 2 or 3) always matches its position on the button press (e.g., the number '1' would appear in the first (leftmost) position). Sample trials are, therefore, 100, 020 or 003. Also inform subjects that during other (interference) trials, in contrast, the target (1, 2 or 3) never matches its position on the button press, and the distractors are themselves potential targets (e.g., 233, correct answer is '2').
Emphasize that subjects are to report what the target number is regardless of its position (see **Fig. 1**).

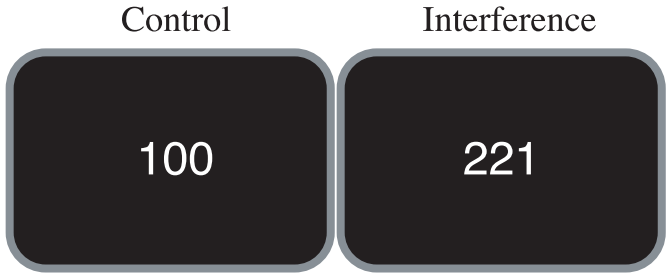

Figure 1 | MSIT trial examples. Subjects are asked to report, via button press, the identity of the number that differs from the other two numbers. During control trials (left), the distractors are zeros (0) and target numbers are always placed congruently with their position on the button box. During interference trials (right), the distractors are other numbers (either 1, 2 or 3), and target numbers are never placed congruently with their position on the button box. In both examples, the correct answer would be to press button '1'.

6| Explicitly instruct subjects: (a) that the sets of numbers will change about every 2 s (actual interstimulus interval for healthy adults is 1,750 ms), and (b) to "answer as quickly as possible, but since getting the correct answer is important, do not sacrifice accuracy for speed."

7| After instructions are reviewed, and just prior to entering the scanner (or being formally tested), subjects should complete a 1-min or 5-min computerized practice version of the task (see guidelines below).
▲ **CRITICAL STEP** Review the responses immediately to ensure that the subject understood the task and can perform correctly, without giving excessive practice. Ensure that subjects are reporting the target number identity and not its position during interference trials (an error that occurs in less than 5% of subjects, but if not caught and corrected during practice will invalidate testing). If subject is found to report position during practice, review results and have them perform practice session correctly before proceeding.

8| Inform subjects that scans will begin and end with fixation of a white dot for 30 s, and that between these times there will be two trial types (some with zeros and some without) that will appear in blocks that alternate every 42 s. Block-formatted fMRI scans start and end with 30 s of fixation on a small dot as it assists in drift correction and between-run assessment by providing a less biased baseline unrelated to the task.

9| Have subjects lie on a padded scanner couch in a dimly-illuminated room, and have them insert foam ear plugs that attenuate high-intensity scanner sounds but allow spoken instructions to be heard well.

10| Stabilize the subject's head via one of the generally used techniques (i.e., foam padding within the head coil, or a plastic bite bar molded to each subject's dentition).

11| Have subjects complete two scans each of the MSIT, where four 42-s blocks of the control trials (C) alternate with four interference (I) blocks, book-ended by 30-s blocks of fixation (F) as described above. Given a fixed interstimulus interval of 1,750 ms, subjects will complete 24 trials during each (neutral/interference) block, 96 trials of each type during a single scan and 192 total trials of each type during the two-scan session (each block type is presented four times for a total scan time of 6 min, 36 s). Pilot data have confirmed that the order of block presentation does not affect results, so we now present the blocks in fixed order: FCICICICIF. However, the block order of presentation can be counterbalanced across runs and subjects.

● TIMING

Subject preparation: approximately 20 min
Scanning and testing: approximately 20 min

? TROUBLESHOOTING

It is critically important to check the practice task results to ensure that subjects understand how to perform the task. It should be noted that the blocked format may not be optimal in every situation, and as indicated previously, researchers should consider using the MSIT stimuli in event-related format as appropriate to imaging modality (e.g., rapid event-related formatting techniques (see ref. 37) can be used to format for fMRI experiments). Lastly, children, elderly adults and some patient groups may perform tasks like the MSIT more slowly. These cases may require pilot testing to establish optimal timing parameters for the subject group in question.

ANTICIPATED RESULTS

Performance

Accuracy in healthy adult volunteers should be expected to be high. The combined mean accuracy for the 25 healthy adults that have been scanned in our lab to date[7,29] was 99.4 ± 1.3% (s.d.) for control trials, and 97.4 ± 2.0% for interference trials. Both accuracy and RT differences between control and interference trials were highly significant ($P < 0.00001$ for both).

RTs are uniformly greater for interference trials compared with control trials—this difference score is the cognitive interference effect ($RT_{interference} - RT_{control}$). In the combined group ($n = 25$), the mean interference effect was large (281 ± 65.2 ms, range 154–420 ms). It generally starts in the 300–400 ms range in adults during the first 5 min and then stabilizes thereafter. The initial validation study[7], designed in part to evaluate early performance and imaging effects, showed that after the first scan, both performance and CFP activation tend to decrease by roughly 30%, but thereafter tend to stay fairly stable (with the cognitive interference effect ($RT_{interference}$) in the vast (majority of cases remaining above 200 ms despite extensive practice). Given these findings, our protocols for single-exposure studies seeking to maximally activate CFP use only a brief 1-min practice session, whereas longitudinal (test-retest) studies or cross-sectional studies seeking to minimize early RT and fMRI signal variance now include an extended 5-min practice session.

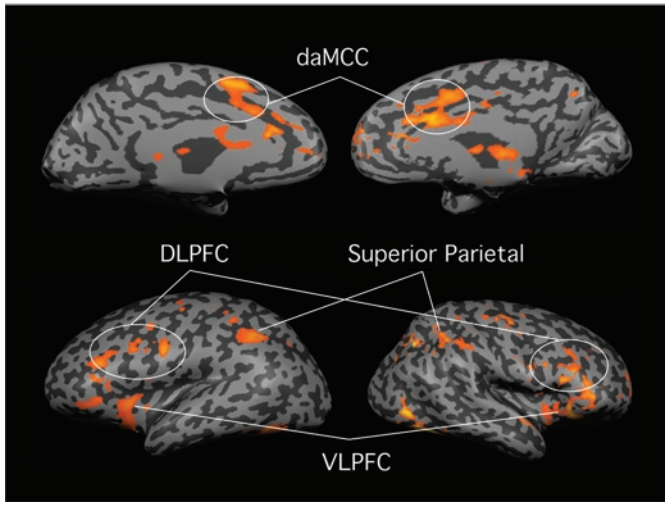

Figure 2 | MSIT typical individual fMRI response. A typical single-scan fMRI response is shown for an individual subject in the inflated view format (light gray = gyri, dark gray = sulci). Note the robust bilateral activation ($P < 10^{-4}$) in the CFP network (daMCC, DLPFC, and superior parietal cortex). Additional activity is often seen, as here, in ventrolateral prefrontal cortex (VLPFC).

Brain responses

The MSIT has been validated in healthy adults[7,29] and interference minus control trial subtractions can be expected to activate the CFP network of brain regions involved in attention, response selection, motor planning and motor output, including daMCC, DLPFC (middle frontal gyri), premotor and primary motor cortex, inferior temporal gyrus and the superior parietal lobule. A typical example of activated regions within a single subject appears in **Figure 2**. These structures subserve cognitive processing in parallel-distributed fashion[5,38,39]. The daMCC contributes to many cognitive processes[1,27,40], DLPFC has often been reported to be coactivated with daMCC during cognitive tasks[2,41–43], premotor cortex is responsible for planning and execution of non-automatic tasks[44,45], and parietal cortex has been shown to be activated during target detection tasks[4,46] and Stroop tasks[8,12,14,17,47]. Although the precise roles these structures play in such tasks remain to be determined, the convergent data argue that they interact as a network, and the challenge ahead is to determine the role of the individual components of these distributed brain circuits. Also, the MSIT typically produces nonspecific 'deactivation' effects in affective regions such as pregenual/subgenual ACC, posterior cingulate cortex and amygdala[1,34].

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