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A Rapid fMRI Task Battery for Mapping of Visual, Motor, Cognitive and Emotional Function

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Abstract

A set of sensory, motor, cognitive and emotional tasks were combined in a simple, rapid-presentation task battery and tested on a group of 31, normal, healthy subjects aged 22 to 76. Five tasks were selected on the basis of widespread use in fMRI and their ability to produce robust and reliable regional activations. They were: 1) a visual task designed to activate the occipital cortex; 2) a bimanual motor task designed to activate motor areas; 3) a verb generation task designed to activate speech processing areas; 4) an n-back task designed to activate areas associated with working memory and executive function; and 5) an emotional pictures task designed to provoke strong emotional responses that typically activate limbic structures. Most of the tasks produced reliable activations in individual subjects, and assessments of the distribution and reliability of individual subject activations in each targeted area are provided. The emotional pictures task did not demonstrate adequate sensitivity in a priori target regions, only in the a posteriori defined inferior temporal region. Age and gender specific differences were found in the activation patterns for both the cognitive and emotional tasks. The battery provides a prescribed means for researchers to obtain reliable functional localizers within 20–25 minutes of scanning, which can be used to support more elaborate mapping studies of brain function. The dataset can also serve as reliability metric for new fMRI labs and novice investigators seeking to test their acquisition and analysis techniques with minimal time investment and expense.

Keywords

fMRI; brain mapping; task battery; sensory; cognition; emotion; aging

INTRODUCTION

Many studies have demonstrated that functional magnetic resonance imaging (fMRI) can reliably activate specific sensory, cognitive and limbic systems within the human brain (Moonen and Bandettini 1999; Cabeza and Nyberg, 2000; Cabeza and Kingstone 2001; Sabatinelli, et al. 2005). Most fMRI studies concentrate on one specific functional system and devote entire scanning sessions to probing its behavior. There are, however, numerous circumstances in which it would be advantageous to collect data from multiple systems within the brain of a single subject. While the time and expense associated with repeated fMRI sessions often discourages such studies, the development of a rapid and reliable task battery that targets multiple systems and can be performed in one study session could be put to use in a wide range of functional imaging applications. These include, for example, the localization of “eloquent”

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speech areas for neurosurgical planning, the establishment of functional activation markers for use in probing more complex regional functions, use as a benchmark dataset for testing in new imaging labs, and deployment as an educational tool for fMRI training. Accordingly, the principle goal of the present work is to demonstrate the viability of acquiring stable and reliable data from multiple brain systems with minimal commitment of scanner time. In the present study we developed a battery of tasks that provides markers of activity in multiple brain systems (i.e. sensory, motor, cognitive and limbic) in individual subjects within a relatively short acquisition time of 2.5 minutes per task, or approximately 12.5 minutes for one run of the full functional battery (apart from the anatomical acquisition).

In clinical practice several paradigms are used to identify the sensory and motor areas (Lee, et al. 1998; Bittar, et al. 1999; Boling, et al. 1999) and language-related areas (Binder, et al. 1997; FitzGerald, et al. 1997; Benson, et al. 1999; Fernandez, et al. 2001). Some batteries have been developed for neurosurgical planning that include multiple, overlapping tasks for motor and language mapping (Tomczak, et al. 2000; Heilbrun, et al. 2001; Haberg, et al. 2004), and one battery includes tasks for motor, sensory and language mapping (Hirsch, et al. 2000). These batteries target regions considered most critical for surgical decisions and are designed for patients with a wide range of symptoms and abilities. Consequently, the clinical batteries are designed to be simple to perform, so that the largest number of potentially impaired patients might comply with task directions, and they are geared to be most sensitive in visual, motor and language areas that surgeons wish to spare to avoid devastating handicaps to patients. Such batteries consequently tend to ignore mapping of limbic and non-language cognitive functions.

The goals of this study were to develop a suite of common behavioral tasks, targeting sensory-motor areas as well as more complex cognitive and emotional functions, and that: a) can reliably localize the visual, motor, language, working memory, and limbic systems *in individual subjects*; b) requires minimal data acquisition time to produce statistically reliable activity within predicted brain areas; c) can be reproduced in any imaging center with standard functional imaging capabilities and basic analysis tools; and d) can be used to produce functional localizers to support cross-laboratory comparisons. While the majority of data reported from fMRI tests are obtained on a relatively young cross-section of the population, mostly college students in their twenties, the present battery was tested on a cohort of subjects with a wider range of ages and educational and cultural backgrounds, thereby providing for an examination of age-based differences, and allowing the results to be generalized to a broader population base. Other factors - such as head motion, task performance and subject compliance - were evaluated to assess their impact on the ability of the task battery to accurately localize brain activity.

METHODS

Subjects

Thirty-one, normal, healthy adults from age 22 to 76 (mean age 41 ± 15.3) were recruited for the study. All subjects were right-handed and fluent in English, with 25 native English speakers. Approximately an equal number of subjects were recruited to form three age groups: those age 30 or less, those 31 to 50 years old and those older than 50. The youngest group of subjects was composed primarily of undergraduate and graduate students, thus providing a basis of comparison with the most common pool of fMRI subjects. All subjects were from the greater Pittsburgh metropolitan area and had at least a high school education, 22% of subjects were college students, 48 % had a college degree and 10% had an advanced degree. A breakdown of the participants by age and gender is presented in Table 1. This study was approved by the University of Pittsburgh Institutional Review Board and performed at the Magnetic Resonance Research Center at the University of Pittsburgh Medical Center. Participants provided written consent and were reimbursed for their time and expenses.

Task Battery

The task battery¹ consisted of four block-design paradigms (Figure 1). All of them had two alternating conditions, a probe and a control, with four repetitions of each (i.e. ABABABAB). The visual and motor tasks were combined into a single, interleaved task, since they activated distinct, non-overlapping functional areas of the brain, and each task could serve as a control for the other. Block duration was set to 18 seconds and run duration was 2 minutes 30 seconds, including two leading acquisitions that were discarded from analysis. In the emotional pictures paradigm a third 6-second block (C) with a fixation cross in the center of a blank screen was inserted between blocks A and B (i.e. ACBCACBCACBC) to avoid carryover effects (i.e., temporal persistence of the induced emotional states). The inter-stimulus interval (ISI) was set at two seconds for all tasks, except the emotional pictures task, which had an ISI of three seconds (Breiter, et al. 1996). Each task was repeated twice, resulting in a total scan time of 25 minutes for the entire battery. The total study scan time, including structural scans and instructions, was about 45 minutes.

The task battery was based on well-established cognitive paradigms known to evoke robust responses in a broad range of subjects. The visual-motor paradigm, consisting of an 8 Hz flashing, radial, checkerboard task (Schneider, et al. 1993; Bandettini, et al. 1997) and a cued, bimanual, finger-tapping task, was based on a similar combined task from a clinical battery used in preoperative planning (Hirsch et al., 2000) that activates primary visual cortex and primary motor cortex in a non-overlapping fashion; therefore, these two tasks were combined into one paradigm with alternating blocks. The verb generation task (Fiez and Raichle, 1997) was based on covert generation of action verbs during presentation of an object cue contrasted with a central crosshair fixation for the control condition. It is known to activate eloquent areas (Broca's and Wernicke's) of speech planning and execution in the dominant, and sometimes non-dominant, hemisphere. The n-back task is a widely-used paradigm (Ragland, et al. 2002; Marshall, et al. 2004) in studies of working memory brain circuitry, and has been shown to activate a number of areas in the frontal and parietal cortices, in particular the dorsolateral-prefrontal cortex (DLPFC). In our implementation of this task a series of letters was displayed one in a time, and subjects were asked to determine if the current letter was the same as that presented two letters previously (2-back). The control condition for this task (0-back) was to search a sequence of letters for pre-specified target, the letter "X". The ratio of target stimuli to distracter stimuli was 1:5. The emotional images task was designed to activate limbic structures such as the amygdala and hippocampus (Breiter, et al. 1996). In this task subjects were instructed to feel the emotions conveyed in a set of emotionally-charged pictures (aggressive, erotic or stressful) from the International Affective Picture System (Lang, et al. 1997), with separate sets of pictures for male and female subjects based on high-arousal scores from the IAPS inventory. Pictures of neutral content, such as geometric figures or furniture, served as a control for this task. Images were presented in random order without repetition.

Subjects were familiarized with the tasks in the battery before their fMRI session. Before each task run instructions were given verbally and via text and pictures on the visual display. Since the n-back task was determined to be the most difficult in pilot studies, participants were able to practice the task before the study for about 5–10 minutes and in the magnet during the acquisition of anatomical images (12 minutes) using an interactive practice routine with variable stimulus presentation rates. In case of incorrect or omitted answers, subjects were presented a sequence of previously presented letters with an explanation of the correct answer. Initially, practice-session participants had up to five seconds before the next letter in the series was presented, but this was increased to a rate of two symbols per second, as in the actual task.

¹The experiment presentation for the entire task battery was programmed in E-Prime software (Psychology Software Tools, Pittsburgh, PA). Contact the second author, S. Baumann, for details to access the software code.

The practice session continued until a subject's performance reached approximately 90% success, usually in less than 12 minutes.

Stimulus Delivery

Stimuli were presented using the IFIS system (MRI Devices Inc, Gainesville, FL) through a 640×480 LCD display mounted on top of a GE Signa headcoil. Subjects were able to receive instructions and communicate with the operator via headphones and a microphone. The subjects' heads were restrained with soft pillows, foam padding and a Velcro band across their forehead. Their responses were collected from both hands using 5-finger, button-response units.

Imaging Parameters

Images were acquired on a GE Signa 1.5 Tesla scanner using a standard volume head-coil. The imaging protocol consisted of: 1) a localizer scan in three orthogonal planes; 2) a high resolution T1-weighted spin-echo scan for in-plane anatomic reference, a 20 cm field of view with 256×256 matrix, providing 37 axial contiguous slices in the AC-PC orientation covering the entire cerebrum with 0.78 mm in-plane resolution and 3 mm thickness; 3) a high-resolution, T1-weighted, anatomic scan for Talairach transformation and surface reconstruction acquired using an SPGR sequence of 124 contiguous slices with $1 \times 1 \times 1.2$ mm voxel resolution; 4) a set of functional images acquired with the same geometric parameters as the T1 inplane reference scan, including number of slices and slice thickness, with a gradient echo T_2^* -weighted EPI sequence, a flip angle of 90° , TR = 3000 msec, TE = 50 msec, field of view = 20 cm, 64×64 matrix, providing 3.1×3.1 mm in-plane resolution. During each functional run 50 EPI volumes were acquired, and the first two volumes were skipped for analysis.

Data Processing and Analysis

Activation maps for individual subjects and group data—The functional data series were analyzed using Brain Voyager QX version 1.3 software (Brain Innovations, Inc., Maastricht, The Netherlands). Data from each functional run were realigned to the first image, motion and slice scan-time corrected, smoothed with a 6 mm Gaussian kernel, and passed through a linear trend removal routine and a high pass filter (0.02 Hz cutoff value). Motion correction utilized an affine, 9-parameter (3 translation and 3 rotation), tri-linear transformation in 3D space. Slice scan-time correction was performed using sinc-interpolation, taking into account TR and slice order, and interpolating the time course of all slices within TR to the time of the first slice acquisition. High-resolution, 3D, structural data-sets were transformed into Talairach coordinate space using the nine-parameter landmark method (Talairach and Tournoux 1988). The high-resolution, reference, spin-echo scan was realigned with the Talairach-transformed, volume, 3D scan. The obtained transformation matrix was applied to all functional series of the recording session.

To test for activations in the imaging data, each task dataset was analyzed with a general linear model constructed using boxcar predictors of the probe blocks, separate for the first and second runs, convolved with a hemodynamic response function. Predictors for control conditions were not explicitly modeled, except for the emotional pictures task, where a direct contrast was conducted between the blocks of emotionally charged and neutral pictures. In the visual-motor paradigm, activation of the task that was not explicitly modeled (visual) appeared as “negative”. For each task in the battery, functional maps were calculated for individual subjects and for the various groups using fixed-effects analysis. P-value thresholding was applied with false discovery rates (Genovese et al., 2002) of $q=0.05$ for the emotional images task and $q=0.01$ for the rest of the tasks in the battery. The same thresholds were used for individual subject and group data analysis, including two-sample t-tests for the age and gender specific contrasts.

Selection of targeted and other reported areas—Regions of interest (i.e. targeted areas) for each task were selected a priori on the basis of typical areas reported in the literature for similar tasks. Targeted areas, specified on Figure 1, were chosen to be specific for the tasks and/or be of special interest, such as the amygdala and hippocampus for the emotional pictures task. Analysis focused on the targeted regions, but coordinates and detection reliability for all significant and sufficiently large clusters observed for the tasks in the battery are reported. Areas were considered activated, if they contained any cluster with more than 50 significant voxels in Talairach space on the individual subject maps. Smaller clusters of voxels were not analyzed. For individuals the centers of activation for each task were calculated using the centroid of the largest voxel cluster in a particular region. For groups the average of the coordinates of the individual subject centroids was used to define the center of activation for a region. The spatial extent and coordinates of activated areas were calculated for each task of the battery.

A combination of functional and anatomical criteria was used to identify targeted areas, with strictly anatomical criteria being applied to identify primary motor cortex, amygdala, hippocampus, cingulate and fusiform gyrus. The rest of the ROIs were identified a posteriori, based on activations obtained from group maps, and in many cases the ROIs were spread over a wide area covering either several anatomic structures (i.e. parietal cortex) or functionally defined areas (i.e. Broca's). Group activation maps were calculated and coordinates of the commonly activated areas were determined. Individual subject clusters were determined to belong to an ROI if they fell within 15 mm from the group cluster center. The value of 15 mm was chosen based on the published inter-subject variability for similar tasks (Seghier et al., 2004), and on our own preliminary data where activated regions for a subset of subjects with different genders and ages were identified according to their relative Talairach coordinates and corresponding anatomical landmarks. Brodmann areas (BA) for these ROIs were determined on the basis of the closest BA reported by the Talairach Daemon (Lancaster, et al. 2000), which accepts single point coordinates and reports BA labels and anatomical structures within a predefined spatial-query range.

Detection of task sensitivity—The sensitivity of a task was estimated as a percent of individuals for whom activation was present in the targeted areas. Second-level, random-effects analysis was used to obtain p-values for group maps. Fixed-effect group analysis, with normalization for signal percent change in each participant (Formisano et al., 2002), was performed to estimate age and gender specific activation for each task of the battery. Contrast maps between groups (oldest vs. youngest and females vs. males) were generated in the context of the general linear model (i.e. a two-sample t-test). A t-test with Bonferroni correction for multiple comparisons was used to compare subject performance and head motion between age groups.

The number of activated voxels for one run or two runs for each task of the battery, and the average p-value for the activation clusters after two combined runs, were obtained after FDR correction. The percent signal change in activated clusters was determined as the maximum amplitude of averaged signal increase for the test blocks relative to the control blocks. Clusters of activated voxels were sampled with spatial extent of 10 voxels in each dimension from the cluster's centroid.

RESULTS

Subject Compliance, Head Movement and Task Performance

Data regarding subject compliance, head movement, and performance are summarized in Table 1. The a priori inclusion criteria required performance with greater than 70% accuracy on each task, and overall head motion of less than 1 voxel in size in any direction. All subjects, even

those in the oldest group, were able to adequately hold their heads still and perform the tasks in the battery, so all subjects contributed data to the analyses. However, one run from a subject in the youngest group and two runs from a subject in the oldest group were excluded due to excessive head motion. Head movement data for each task was obtained as an output of the image realignment step, and the maximal head movement from any of the tasks was used for analysis. In all age groups the most movement was observed along the z-axis in the head-foot direction (2.1 ± 1.1 mm) as well as in pitching the head backwards (2.3 ± 1.9 deg). This likely related to neck-muscle relaxation during the experiment, and it can gradually reach a displacement of several millimeters from the original position. Head movement was not significantly different between the two younger groups. However, head movement was significantly larger in the oldest group compared to the two younger groups ($t_{20}=7.56$, $p<0.001$), and may reflect less muscle tone in the elderly. Since head displacement, even in the oldest group, was generally gradual, without abrupt movement and less than 1 voxel size, it was adequately corrected by the motion correction routine (as inspected by sequential visualization of the motion corrected images).

Subject performance was assessed in two tasks, visual-motor and working memory, where subjects had to respond on cue by pressing a button on the response boxes. Responses for the visual-motor task were 95–96 % correct across the three groups and not statistically different between them. In the more difficult working-memory (n-back) task, performance of the oldest group (78.4 ± 6.3 % correct in test run 1 and 81.6 ± 5.6 % correct in test run 2) was significantly lower than in the other two groups, whose scores were very similar to one another.

Observed Activation and Test Sensitivity

The purpose of each task in the battery was to activate the targeted region(s) of interest as specified in Figure 1. The sensitivity of a task was determined as a percentage of individual subjects showing activity in the targeted regions. These sensitivity data are presented in Table 2 with corresponding Talairach coordinates of the group activation centers. The data are shown for the areas with moderate to high sensitivities. Typical functional maps for both individual subjects and group averages are presented in Figure 1.

The task battery was able to activate most of the areas reported in similar individual studies (Cabeza and Nyberg, 2000). The activated regions in Table 2 are based on anatomic locations in individual subjects, grouped by a common relative position in the brain. Brodmann areas are reported in parentheses, and correspond to the group average for a given activated region of interest.

In the visual-motor tasks the targeted areas (shown in Figure 1) were the primary motor cortex bilaterally (hand area in precentral gyrus of BA 4), the supplementary motor cortex (dorsomedial frontal cortex of BA 6) and the primary visual cortex bilaterally (calcarine sulcus in BA 17/18). Activation in primary motor and visual cortex was very robust and was observed in all subjects after only the first run of the task (see Table 4). Task sensitivity to the supplementary motor cortex was also high at 90% after the first run and 100% after the second run for all subjects.

In the verb-generation task the targeted areas in the dominant left hemisphere (see Figure 1) were the inferior frontal cortex (Broca's area, BA 44/45) and the superior temporal cortex (Wernike's area, BA 22/42) with 97% and 81% sensitivity, respectively (see Table 2), but only after two runs (see Table 4). Both of these language-related areas exhibit high sensitivity, even though there was no overt speech production in the task. Less robust activation in several additional areas was observed for the task (see Table 2), such as the left middle frontal cortex (BA 6/8/9) with 81% sensitivity, the cingulate gyrus (BA 6/24/32) with 72% sensitivity and the left parietal cortex (B/A 7/39/40) with 58% sensitivity. Interestingly, about a third of the

subjects, all of whom were right-handed, showed activation in homologous areas in the right hemisphere.

The working memory n-back task produced highly reliable activation (see Table 2) in the dorsolateral prefrontal cortex (DLPFC, BA 9/8/46) with 84% sensitivity for the left DLPFC and 74% for the right DLPFC, 83% sensitivity in the left cingulate (BA 6/24/32) and 81% sensitivity in the left precentral cortex (BA 6/32). These are areas previously reported to be responsible for working memory and attention functions (Cabeza and Nyberg, 2000). Less reliable activation was detected in other areas of the bilateral prefrontal (BA 10, 51% sensitivity), bilateral inferior frontal (BA 44/45, 55% and 32% sensitivity) and parietal cortex (BA 7 and BA 39/40) with 61% and 58% sensitivity, respectively, for the left and 52% and 74%, respectively, for the right. Many of the areas showed a decrease in activation with age that was quite pronounced in the left DLPFC (BA 9/8/46), the left medial parietal cortex (BA 39/40), the left cingulate (BA 6/24/32), and bilaterally in the inferior frontal cortex (BA 44/45) and the precentral gyrus (BA 6).

The contrast between emotionally charged and neutral pictures in the emotional pictures task produced multiple foci of moderate activation with the strongest bilaterally in the inferior temporal cortex (BA37), showing 80–87% sensitivity (See Table 2). Comparatively moderate activation was observed bilaterally in the inferior occipital cortex (BA 18/19). Activation in the targeted areas of the amygdala and hippocampus was detectable less often in only 29–48% of the subjects, and activation generally was weaker than that in other tasks of the battery.

Effect of Subject Performance on Activation Patterns

For the language and emotional imagery tasks, there was no feedback from subjects during or following task execution, so we could not assess subject compliance for those tasks. For the visual-motor and n-back tasks, after the practice runs subject compliance across all age groups as assessed by cued feedback was high (Table 1). Performance on the n-back memory task across all subjects did not show any significant correlation between number of correct answers in control and test blocks and number of voxels, average p-value, or percent signal change in DLPFC. However, performance in the n-back memory task was significantly lower in the oldest group for the test blocks (Table 1), and the task elicited more activation in the DLPFC and parietal cortex reflecting more workload for the elderly subjects. In the current design of the memory task it was not possible to tell if lower performance was caused by insufficient effort or inability of the subjects to perform the task.

Variability of Individual Activation Center Locations

For each subject we identified a single point, the centroid of the cluster with the strongest activation, representing the location of each targeted area in Talairach space, and these points varied among subjects. Boundaries covering 100% of the centroids for each region of interest (ROI) are shown on the scatter plots in Figure 2. (Note that activation centers for some subjects are absent, since they did not have clusters of at least 50 voxels for those tasks. Consequently, the number of points contained within some bounded ROIs is less than 31.) Relatively compact clusters cover the visual and motor cortices from the combined visual-motor task (row A), the left inferior frontal cortex and the inferior temporal cortex from the language task (row B), and the amygdala and hippocampus from the emotional pictures task (row E). The widest spread of individual subject activation was observed in frontal cortex and associative parietal cortex from the working memory and emotional pictures tasks (rows C, D and E).

To determine the reliability with which targeted areas can be identified among subjects using automated, atlas-based coordinate systems (e.g. Talairach daemon software), the distance from the centers of activation for each subject to the corresponding BAs were determined by

gradually increasing the search range in the software database. Table 3 shows the probability that activation for each task falls inside selected Brodmann areas (BAs) that are well-established functional loci for these tasks. For example only 45 % of the activation centers for the motor task were found inside the left Brodmann areas 3 and 4 (primary motor cortex) as defined on the Talairach atlas, but 94 % of the centers were found within 7 mm of the target areas and 100% within a range of 11 mm. This data suggests relatively high individual variability for hand representation in the motor cortex and high variability for the position of the precentral gyrus itself. This is supported elsewhere by the finding of large spatial variability in the cytoarchitectonic representation of BA4 (Rademacher et al., 2001). Nevertheless, localization of the hand area in individual subjects can be highly reproducible between sessions, as shown by our own data (Table 4) and that of Marshall et al. (2004). The probability of finding activation peaks in the right primary motor area is comparable, but it is considerably higher for the supplementary motor and primary visual cortices and reaches 100% within only 3mm from the supplementary motor area (BA 6) and 87% to 97% within 5 mm bilaterally for the primary visual cortex (BA 17/18). Although the flashing checkerboard task evoked strong and extensive responses in the visual cortex, it took 7mm of the search range from BA17/18 to cover 100% of the activation centers. This can be explained by the fact that the flashing checkerboard paradigm activates large areas in both the primary and secondary visual cortex, and the centroid of activation may be located not in primary, but in extended secondary visual cortex

The most variable individual locations were observed for language production and execution centers. The language task produced robust and reliable activation in the inferior frontal cortex, observed in 94% of tested subjects, but localization of language centers had relatively high variability for individuals, especially for Broca's area. Only 35% of the activation centers in Broca's area fell into Brodmann areas 44/45, and only 42% of the activation centers in Wernicke's area fell into BA 22/42; but for Broca's area increasing the search range to 11mm covers 94% of the activation centers.

The working memory task produced less individual variability in bilateral activation of the DLPFC, showing 100% of the individual centers of activity within 7 mm. Inferior frontal and parietal cortex show large overlap in the n-back and verb generation tasks, an indication of shared circuitry during phonological retrieval, semantic decision and working memory tasks (Muller and Basho, 2004).

Signal Change and Activation Strength in the Targeted Areas

Table 4 summarizes the activation results from one run and from two runs for each of the tasks in the targeted areas. The false discovery rate (FDR) was applied to correct p-values and to threshold functional maps. Activation of a cluster in one of the target regions was determined on the basis of 50 or more contiguous voxels appearing above threshold at the listed p-value. Clusters were sampled with a spatial extent restriction of 10 voxels in each dimension as selected in the Brain Voyager interface. (This is actually 11 voxels in the software calculations, so that an upper limit of $11 \times 11 \times 11 = 1331$ voxels could have been exceeded for some areas of larger extent, such as in the primary motor and visual cortices.) One run was sufficient only in the combined visual-motor task to reliably activate targeted areas for all the subjects. Two runs were necessary to reliably activate the targeted areas for the cognitive tasks, but even two runs was not sufficient to reliably activate half of the subjects for the targeted regions in the emotional pictures task, perhaps because of the smaller spatial extent of the signal as shown by the number of activated voxels. However, Table 2 indicates that a non-targeted region in this task, the inferior temporal cortex bilaterally, had a high sensitivity. Recent work (Sabatinelli et al., 2005) indicates that this region is activated in visual emotional tasks and therefore should have been included as a target region.

Signal change in the activated clusters varied from 0.8 to 1.9% for the different tasks of the battery and was largest in the motor and visual cortex, as expected. Interestingly, average signal increase for these areas seems comparable with that in the less consistently activated amygdala and hippocampal areas. However, this apparent contradiction is explained by recognizing that a larger number of weakly active voxels pass the significance threshold in the visual-motor task, whereas signal change in the center of clusters was much stronger at 3–5%.

Age and Gender Specific Activation

There was no significant age or gender difference for group activation in the visual–motor paradigm. Also, no significant gender difference for group activation was detected in the language and working memory paradigms. However, upon testing the difference in activation patterns between the youngest and the oldest groups, the working memory task revealed relatively greater BOLD signal of the medial prefrontal cortex, parietal cortex, and posterior cingulate in the oldest vs. the youngest group (Figure 3A). Similarly, for the verb generation task relatively greater BOLD signal in the oldest group (Figure 3C) was detected in frontal (BA 10), left DLPFC (BA 9/46), posterior cingulate cortex (BA 23), parietal cortex, precuneus (BA 7), and the parahippocampal gyrus (BA 23) when compared to the youngest group.

However, analysis of the signal changes showed that stronger “activation” in the posterior cingulate and prefrontal cortex is in fact deactivation in these areas for the youngest group (Figures 3B and 3D). For the working memory task, beta values, corrected by confound (i.e. percent signal change), were -0.69 in the prefrontal cortex and -0.45 in the posterior cingulate for the youngest group. There was no significant signal change in these areas for the oldest group. In the parietal cortex beta values were -0.35 for the youngest group and 0.45 for the oldest group. For the verb generation task beta values in the medial frontal cortex were -0.60 and 0.26 , respectively, for the youngest and oldest groups; beta values in the posterior cingulate were -0.60 for the youngest group and -0.03 for the oldest group. Thus, the age differences for the working memory task in the parietal cortex and for the verb generation task in the medial prefrontal cortex region are explained by deactivation in the youngest group *and* true activation in the oldest group.

This agrees with previous reports which have shown that a specific set of regions in young adults consistently shows deactivation when the signal in a probe condition is less than the signal in a baseline condition, and this phenomenon generalizes across a wide range of tasks and stimulus modalities (Shulman et al., 1997; Mazoyer, Zago et al. 2001; McKiernan, Kaufman et al. 2003; Lustig et al., 2003). These commonly deactivated regions include large sections of the lateral parietal cortex, the medial parietal cortex (including the posterior cingulate and precuneus), and the medial frontal cortex. The functional significance of these deactivations remains unclear. One current hypothesis is that the regions involved constitute a default network supporting processes more active during passive than active-task conditions (Raichle et al., 2001).

In the emotional pictures task there was a significant ($p < 0.05$) gender and age difference. Females had stronger activation in the occipital cortex (BA17/19), and males had more extensive activation in frontal cortex, the inferior temporal gyrus (BA 37), the middle temporal gyrus (BA21), the posterior cingulate, and the amygdala. A similar pattern of gender difference for activation in emotional picture perception has been reported by others (Wrase et al., 2003; Sabatinelli et al., 2004). Comparison of the age dependent responses in our own data for the emotional pictures task shows relatively high absolute activity in the amygdala, left parahippocampal gyrus and ventral occipital cortex (BA 18,19) in the youngest group, and left inferior frontal and left temporal gyri (BA 47) in the oldest group. These observations are in agreement with previously demonstrated greater activation in younger versus older individuals in the right amygdala/hippocampus region, whereas older adults demonstrated greater

activation in the right anterior-ventral insula cortex in an emotional faces task with the angry versus neutral faces contrast (Fischer et al., 2005).

DISCUSSION

A set of “classical” sensory-motor, cognitive and emotional tasks was combined in a task battery and tested on a group of normal, healthy subjects across a wide range of ages in an effort to design a set of tasks that can be administered quickly to obtain prototyping data for fMRI studies. The functional portion of the battery can be administered in approximately 20–25 minutes, and with additional modifications the battery might be even shorter. All of the tasks were successful in activating at least one distinctive region of interest specific to the tasks for 100% of the younger participants and for at least 80% of all the participants. Age is a significant factor for some of the tasks with a gradual decrease in sensitivity in most of the ROIs with age. The battery can provide a standardized database of functional brain activity for established paradigms. The high sensitivity for younger subjects makes the battery particularly suitable for many fMRI studies of healthy subjects, which are largely performed on subjects under the age of 31, and who comprise most of the population of undergraduate and graduate students from whom normative-fMRI study participants are often selected.

The task battery was inspired by a clinical task battery (Hirsch et al., 2000) routinely used in presurgical, functional mapping at Memorial Sloan Kettering Cancer Center. That battery is based on a simple pedestal design, with one active block surrounded by baseline blocks, which facilitate simple and rapid execution of the task battery for a wide clinical population with possible deficits. In our battery we include more complex tasks that can be executed by all age groups, and include more repetitions of active and baseline blocks. This design is more demanding to the subjects, but is known to be more resistant to linear noise trends and to provide better signal-to-noise ratio resulting in more selective activation (Huettel, et al. 2004).

One of the results of this study is the surprisingly large between-subjects variability in locations and spread of the activation for a given task, especially in the frontal cortex. Large between-subjects variability previously has been reported for a language task (Seghier, et al. 2004) and a working memory task (Wei, et al. 2004). The observed variability of activations across groups and cortical areas can be explained by a combination of anatomic variability in gyri formation (Ojemann et al., 1989; Woods et al., 1999) and individual cognitive strategy (Nadeau, Williamson et al. 1998). While primary visual and motor cortices are more anatomically localized (Rademacher et al., 1993), language, memory and emotional tasks involve more distributed neuronal networks in association cortex (Steinmetz and Seitz, 1991). Larger inter-subject variability in activation patterns, relative to a motor task, has been reported for a working memory task (Marshall et al., 2004) and for a semantic retrieval task (Seghier et al., 2004). Moreover, regions of more frequent activation, such as prefrontal cortex, appear to become more compact with less inter-individual variability, as opposed to occipito-parietal cortex, where activation is observed less frequently and which is more widespread (Seghier et al., 2004).

An additional source of inter-subject variability results from the between-subject normalization technique. A simple, piecewise, nine-parameter landmark method of Talairach and Tournoux (1988) was employed. Although this technique provides robust normalization of individual subject anatomy to the standard coordinate space, it makes no effort to match brain surface gyri and sulci patterns. Variability of the activation locations in Talairach space due to gyri variability can be reduced by applying more sophisticated normalization techniques with non-linear warping (Crum et al., 2003). Monitoring of head motion is critically important to ensure robust and reproducible activations. Distributions of the individual activations were obtained for each task as shown in Figure 2. These ROI maps can be used for development of automated

algorithms for quality assessment of fMRI data. Variability of activation pattern among individual subjects raises the important issue that even for known areas, such as motor and language centers, each subject must be tested individually to locate accurately these eloquent areas. This is a well-known phenomenon and the very reason why individual maps are used for preoperative planning (Hirsch et al., 2000; Tomczak et al., 2000; Heilbrun et al., 2001; Haberg et al., 2004).

Development of future task batteries should include methods to allow monitoring subject performance and to control subject compliance. This can be accomplished by collecting and scoring subject responses as correct or incorrect, as was done for several of the tasks in this battery, but not for the verb generation task or the emotional pictures task. Compliance for the verb generation task might be measured by a post-task test to assess recognition of the presented nouns, overt speech production during the task (although this might increase head motion) or by employing a multiple choice test that requires a button press for the correct verb (though these changes may produce an inadvertent change in the locus of each activation). Similar strategies to control subject compliance can be employed for the emotional pictures task, as well as use of eye-tracking equipment.

Additional refinements might allow the length of the battery to be decreased further by combining at least two more of the tasks, for language and memory, and using them as a control for one another as is done in the visual-motor task. Currently, the verb generation and n-back tasks overlap somewhat in the left DLFPC/Broca's area and minimally in the left parietal association/Wernicke's area (see Figure 2, rows B, C and D). The verb generation task in our battery is essentially a phonological-retrieval memory task and less a speech production task. If subjects were required to overtly say the answer softly, it might further stimulate the speech execution network, as well as provide desirable feedback to insure subject compliance. Ideally, to minimize visual activation control blocks should be modified to match the probe blocks by employing a meaningless combination of letters. Further separation of activated ROIs for these tasks might be accomplished if the memory load for the language task were increased by making phonological retrieval more difficult. Such a combined task would activate all of the targeted areas for both language and memory.

The n-back task is a popular tool to investigate working memory due to its simplicity and ability to quantitatively change workload. The task robustly activated working memory brain areas across all age groups. However, in this cohort containing different age groups, the n-back task posed the most difficulties in terms of understanding and performance, and it required considerable practice time for some subjects. A special, pretest, instructional-and-practice paradigm was used, and the subjects could practice the task during structural scans. After subjects learned the task, the majority of them were able to execute it with more than 80 % accuracy. It might be improved with minor modifications, such as replacement of letters for the presentation stimuli with objects, and by use of an adjustable presentation rate to simplify task understanding and execution.

The emotional pictures task produced relatively weak activation in the targeted amygdala and hippocampus areas with detection levels lower (30–40%) than other tasks of the battery (80–100%) on an individual subject level. Theoretically, the sensitivity can be improved by longer task durations and by individually tuning the set of presented pictures, based on individual subject emotional responses before imaging sessions (Lang, et al. 1998). In the later case, subjects would have to be scanned after a sufficiently long period of time to preserve novelty and to produce a high emotional response. Thus, in its present configuration this one task in the battery cannot be recommended as a reliable tool for cross-laboratory comparisons targeting the amygdala or the hippocampus, but the task is effective in activating the inferior temporal region with 100% sensitivity in younger subjects and 80–87% sensitivity overall. Recently,

this region has been implicated as part of a network of structures involved in processing arousing emotional stimuli (Sabatinelli et al., 2005). Increasing the number of runs might improve the detection level of the targeted structures, but this may cause subject habituation to the task. It is unlikely that all subjects (i.e. 100% detection level) will show activation in the amygdala and hippocampus using a short paradigm as described here, due to the small spatial extent of the signals. The use of coronal slices for these anterior subcortical areas that are less prone to susceptibility artifact might also improve the likelihood of showing activation (Sabatinelli, et al. 2005).

There were no significant gender effects across visual, motor, language, and memory tasks. Certain age-related differences in these tasks were present, but did not affect the ability of the battery to identify and standardize activity in the targeted areas. Hence, the task battery is robust and reliable across gender and a broad range of ages. The current implementation of the emotional task shows poor sensitivity in the amygdala and hippocampus, and it was further compromised in that it showed significant age and gender effects on activation patterns.

The database provided here can be used as a reference for newly established fMRI centers and for developing standardized sensory, cognitive and clinical datasets. Although admittedly small, containing only 31 subjects, it is a start in the process of providing normative data for healthy subjects of both genders and across a large range of ages in the general population.

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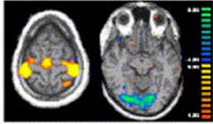
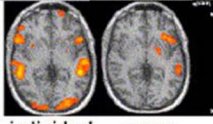
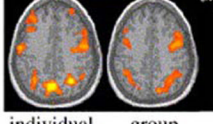
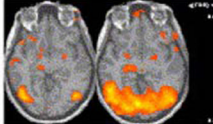
Condition A (probe)	Condition B (control)	Targeted Areas	Representative Slices
Visual - Motor Task (combined)			
Full field radial checkerboard with continuous reversing @ 8 Hz	Bimanual finger press to visually presented cue for finger number	Primary and supplementary motor cortex; primary visual cortex	 motor visual individual maps
Language Task (Verb Generation)			
Think of an appropriate action verb to a presented object noun (i.e. "nail" -> "hit")	Fixate on centrally positioned crosshair	Broca's and Wernicke's areas	 individual group
Working Memory Task (Verbal N-Back)			
2-Back: identify target trials where the current letter matches the letter that was presented 2 trials before	0-Back: search sequence of letters for pre-specified target (letter "X")	Dorsolateral prefrontal cortex	 individual group
Emotional Pictures Task			
Set of emotionally charged pictures (aggressive, erotic or stressful) with high arousal scores from IAPS	Set of neutral pictures (common objects or scenes) with low arousal score from IAPS	Limbic structures: amygdala and hippocampus	 individual group

Figure 1.

Description of tasks within the battery. Two of the tasks, visual and motor, were combined into one to save time. Each task consisted of six alternating blocks, A and B, except for the emotional pictures task in which an additional, six-second, fixation interval was inserted to prevent carry-over effects. Each task lasted 2.5 minutes and was repeated twice (i.e. two runs). Group maps were calculated using a random effects model. A representative map from a single subject is shown for the combined motor and visual tasks, which showed strong activation in one run, while both an individual and a group average map are shown for the other tasks, which required two runs to show significant activation.

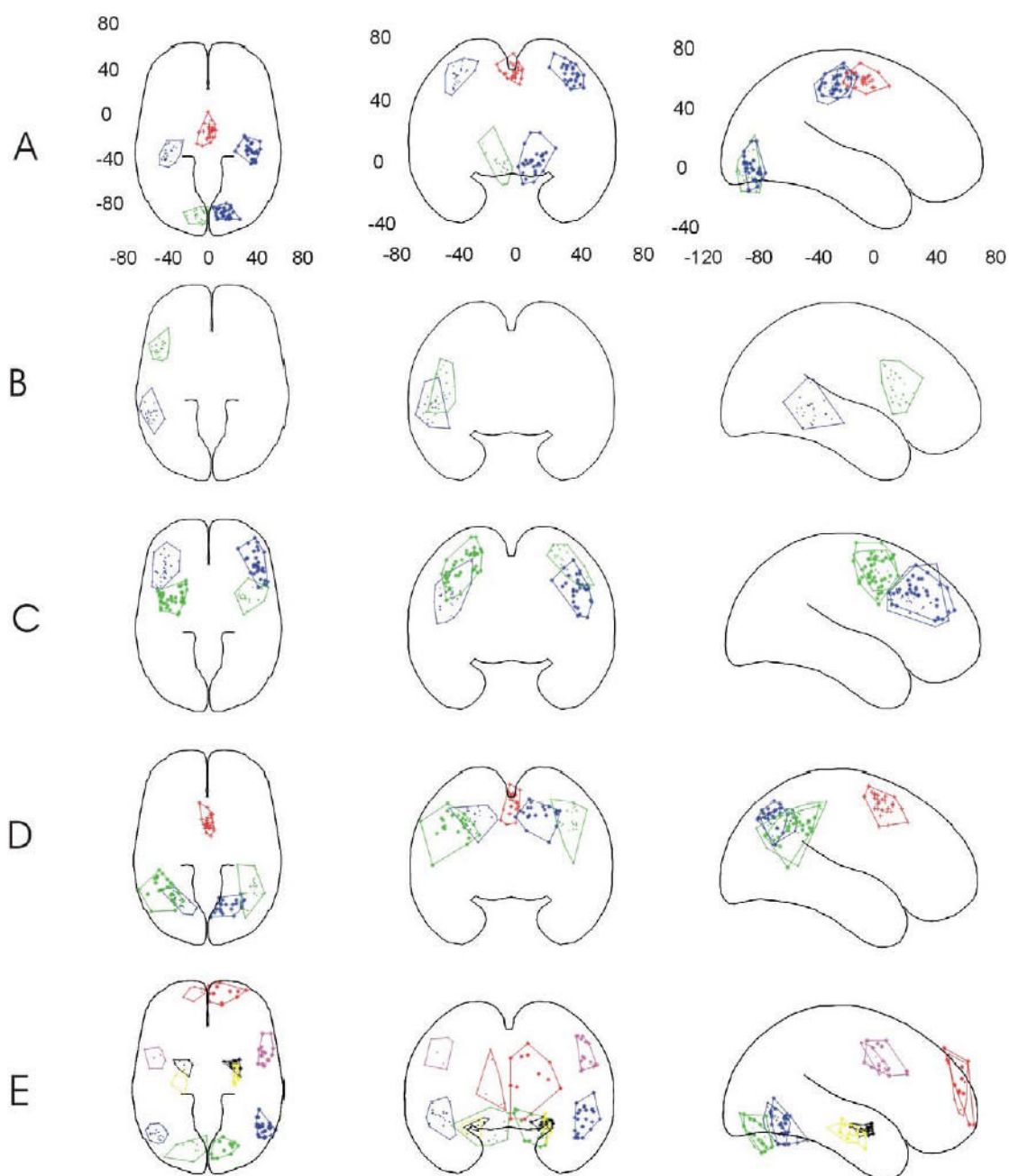


Figure 2.

Orthogonal projections of centers of activation clusters for individual subjects. Each targeted area from an individual subject is represented by a single point corresponding to the centroid of the cluster with the strongest activation. Areas of activation for each task are: **A)** *visual-motor combined task* - primary motor, supplementary motor and visual cortex; **B)** *verb generation task* - Broca's area (left inferior frontal gyrus) and Wernicke's area (left superior temporal gyrus); **C)** *working memory task* - dorsolateral prefrontal and medial frontal cortex; **D)** *working memory task* - parietal and cingulate cortex; **E)** *emotional pictures task* - prefrontal cortex, medial frontal cortex, amygdale, hippocampus, and inferior occipital cortex.

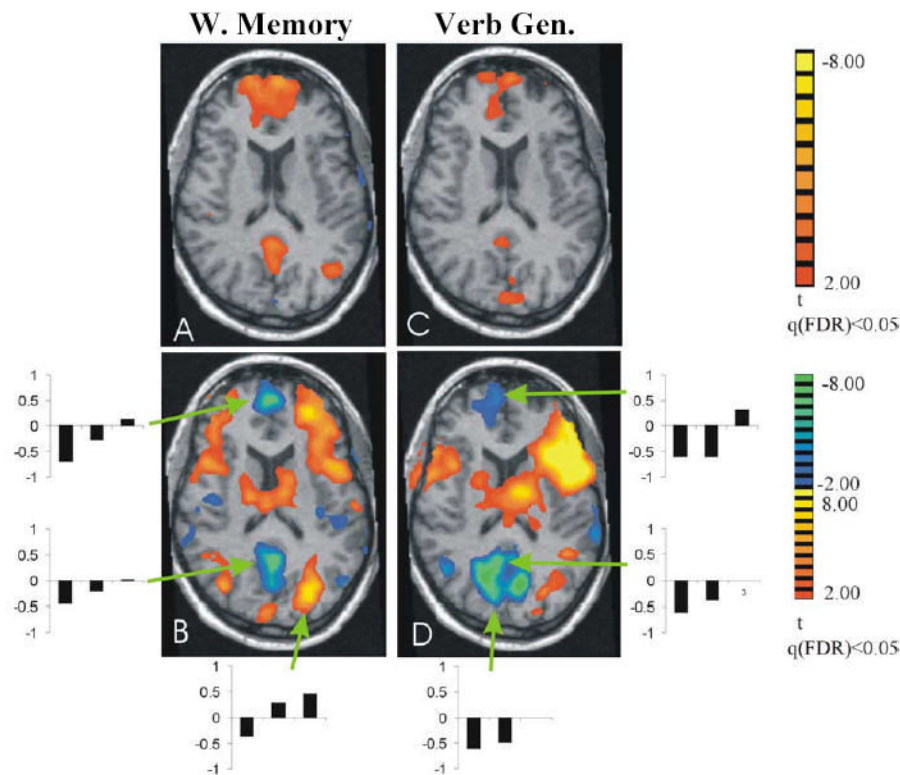


Figure 3.

Age differences in two tasks. (A) Working memory task revealed areas of relatively greater BOLD signal with age in the medial frontal cortex, posterior cingulate and parietal cortex. (B) Negative activation (i.e. deactivation) shown on the same slice as in (A) from one-sample t-test group analysis reveals that these “activations” can be explained by deactivation of the areas in the youngest group. This was confirmed with analysis of signal changes. Bar graphs shows beta values, corrected by confound (% signal change) for the youngest, middle and oldest age groups (from left to right, correspondingly) for the “activated” regions on (A). The age difference in parietal cortex activation is both a true activation in the elderly group and a relative deactivation in the youngest group. (C) Verb generation task revealed greater activation with age in DLPFC (not shown on this slide), medial frontal cortex, parahippocampus and posterior cingulate. (D) Similar to (B), negative signal change in the youngest group explains age-related difference in activation of parahippocampus and posterior cingulate. However, analysis of signal changes, displayed as age groups’ betas, reveals that age difference in medial frontal cortex activation is both a true activation in the elderly group and a relative deactivation in the youngest group. Color indicates p-values according to the color bars on the right in which red colors correspond to positive betas and blue colors to negative betas.

Table 1
Subject demography, head movement and task performance

Age group	< 31	31–50	> 50	All ages
# subjects	10	12	9	31
mean age	24.9±2.5	40.9±9.2	63.7±8.4	40.9±15.4
males/females	4/6	8/4	4/5	16/15
Head translation (mm)				
left-right (x axis)	0.5±0.3	0.7±0.7	1.7±2.57 *	0.9±1.3
anterior-posterior (y axis)	0.8±0.6	0.9±0.7	0.7±0.78	0.8±0.7
head-foot (z axis)	2.3±1.0	1.6±0.8	2.9±1.2	2.1±1.1
Head rotation (degrees)				
pitch (x axis)	2.8±2.5	1.6±1.05	3.0±2.0	2.3±1.9
yaw (y axis)	0.5±0.4	0.5±0.41	1.2±1.9	0.7±1.0
roll (z axis)	0.8±1.4	0.9±0.87	1.6±2.7 *	1.0±1.6
Visual- Motor task:				
% correct	97.3±2.3	98.2±1.9	95.1±3.1	96.8±3.7
N-Back run1: % correct				
control block	94.8±4.3	97.6±3.6	87.3±13.0	94.4±7.9
test block	90.7±6.7	94.1±6.50	78.4±6.3 *	89.5±8.9
N-Back run2: % correct				
control block	93.2±11.3	96.8±3.2	92.1±9.3	94.6±8.0
test block	93.7±3.9	92.4±8.9	81.6±5.6 *	90.4±8.3

* t-test indicates significant difference from other groups, $p < 0.01$

Table 2

Sensitivity of tasks and Talairach coordinates of activated regions. Sensitivity of a task is a percentage of subjects showing activation in selected regions after two runs. Clusters of 50 or more contiguous voxels in Talairach space were necessary to identify a targeted area. Talairach coordinates are shown for: a) the mean cluster center for all subjects (determined as an average of the activation centers among individual subjects); b) distance for x, y, z, in mm from the clusters' centers to boundaries that cover 100 percent of individual subject activation centers; c) group analysis centers determined by random effects GLM. Asterisks (*) indicate a priori identified target areas.

Anatomical Brodmann regions for each task	Sensitivity in age groups				Talairach coordinates		
	All (n=31)	<31 (n=10)	31–50 (n=12)	>50 (n=9)	Mean Cluster Center (x, y, z)	Range for 100% Boundary (x, y, z)	Group analysis centers
Visual-Motor task							
*Primary motor, left (BA 4)	100	100	100	100	–34,–29,52	12,13,13	–32,24,50
*Primary motor, right (BA 4)	100	100	100	100	37,–27,53	13,13,13	38,–26,50
*Supplementary motor (BA 6)	100	100	100	100	1,–10,55	11,17,11	2,–9,56
*Primary visual, left (BA 17/18)	100	100	100	100	–8,–85,–6	14,8,25	–19,–85,8
*Primary visual, right (BA 17/18)	100	100	100	100	14,–83,–3	14,9,18	18,–84,8
Verb generation task							
*Inferior frontal, left (BA 44/45)	97	100	92	100	–44,13,19	10,17,18	–43,10,20
Inferior frontal, right (BA 44/45)	42	30	50	44	49,14,12	11,15,19	
*Superior temporal, left (BA 22/42)	81	90	75	78	–52,–44,4	12,22,20	–55,–35,4
Superior temporal, right (BA 22/42)	29	30	25	33	53,–34,6	13,8,11	
Cingulate (BA 6/24/32)	77	80	75	78	0,1,58	5,12,14	0,7,50
Parietal, left (BA 7/39/40)	58	50	58	67	–40,–51,39	14,15,27	
Parietal, right (BA 7/39/40)	16	20	17	11	44,–46,48	15,16,10	
Middle frontal, left (BA 6/8/9)	81	80	83	78	–42,3,39	9,33,23	
Middle frontal, right (BA 6/8/9)	39	30	42	44	51,–2,41	20,22,15	
Working memory task							
*DLPFC, left (BA 9/8/46)	84	100	83	56	–40,21,31	14,26,21	–38,15,31
*DLPFC, right (BA 9/8/46)	74	80	83	67	42,28,35	16,23,18	44,7,35
Inferior frontal, left (BA 44/45)	55	70	58	33	–46,12,13	11,8,15	–47,13,15
Inferior frontal, right (BA 44/45)	32	50	33	11	47,13,12	9,12,13	
Precentral, left (BA 6)	81	90	83	67	–32,–3,49	13,16,22	–36,–4,43
Precentral, right (BA 6)	65	80	67	44	34,–1,53	19,16,17	32,–2,50
Prefrontal, left (BA 10)	51	50	50	56	–29,52,16	12,14,18	–28,49,16
Prefrontal, right (BA 10)	51	60	50	44	34,57,14	8,13,19	35,43,24
Cingulate, left (BA 6/24/32)	83	90	100	56	1,5,52	8,17,15	3,11,47
Dorsal parietal, left (BA 7)	61	60	75	44	–24,–63,42	17,13,17	–9,–70,40
Dorsal parietal, right (BA 7)	52	40	66	44	19,–68,44	16,10,19	11,–71,42
Medial parietal, left (BA 39/40)	58	80	75	11	–37,–54,37	23,19,27	–30,–58,37
Medial parietal, right (BA 39/40)	74	80	83	56	39,–52,40	13,27,29	34,–57,37
Emotional pictures task							
*Amygdala, left	48	50	33	67	–19,–7,–10	10,10,14	–17,–6,–8
*Amygdala, right	42	40	50	33	21,–6,–9	9,7,12	21,–3,–5
*Hippocampus, left	39	40	42	33	–23,–22,–13	8,10,8	–19,–22,–6
*Hippocampus, right	32	40	50	0	23,–24,–8	8,7,16	22,–24,4

Anatomical Brodmann regions for each task	All (n=31)	Sensitivity in age groups			Mean Cluster Center (x, y, z)	Talairach coordinates Range for 100% Boundary (x, y, z)	Group analysis centers
		<31 (n=10)	31-50 (n=12)	>50 (n=9)			
Parahippocampal, left (BA 34/37)	29	30	42	11	-20,-31,-14	5,21,9	
Parahippocampal, right (BA 34/37)	42	60	25	44	24,-33,-13	11,15,11	25,-26,-1
Fusiform, left	45	60	50	22	-34,-42,-16	11,15,10	-35,-53,-11
Fusiform, right	19	44	8	11	34,-45,-19	13,15,9	43,-45,-13
Inferior occipital, left (BA18/19)	47	70	42	25	-11,-79,-15	26,13,17	-13,-80,-8
Inferior occipital, right (BA18/19)	50	60	42	50	15,-79,-10	12,10,28	6,-78,-10
Inferior temporal, left (BA37)	80	100	75	63	-43,-67,-5	10,9,15	-43,-69,-7
Inferior temporal, right (BA37)	87	100	83	75	47,-62,-6	11,16,18	48,-58,-9
Medial frontal, left (BA 6)	27	40	17	25	-43,0,39	11,10,11	-38,6,30
Medial frontal, right (BA 6)	50	80	17	63	49,4,39	7,17,12	49,14,30
Inferior frontal, left (BA 9/44/45)	27	20	25	38	-42,17,11	7,14,21	-33,19,18
Inferior frontal, right (BA 9/44/45)	43	40	33	63	46,25,13	10,21,26	46,24,19
Prefrontal, left (9/10)	33	10	58	25	-8,57,17	13,8,25	
Prefrontal, right (9/10)	37	20	50	38	14,57,21	19,11,27	3,52,29

Table 3

Probability that individual activation centers in the tasks fall inside, or within a distance from, selected Brodmann areas (BAs). Nearly all subjects showed activation within approximately a centimeter of the listed Brodmann areas.

	Inside	3 mm	5 mm	7 mm	9 mm	11 mm
Motor						
Primary motor cortex, left (BA 3/4)	45	55	64	94	94	100
Primary motor cortex, right (BA 3/4)	42	64	74	81	97	100
Supplementary motor (BA 6)	39	100	100	100	100	100
Visual						
Primary visual, left (BA 17/18)	29	58	87	100	100	100
Primary visual, right (BA 17/18)	26	68	97	100	100	100
Language						
Broca's area (BA 44/45)	35	42	52	74	79	94
Wernicke's Area (BA 22/42)	42	71	74	81	87	90
Working memory						
Dorsolateral prefrontal cortex (BA 9,46)	39	77	94	100	100	100
Emotional pictures						
Amygdala	29	45	64	74	90	100
Hippocampus	32	39	45	52	97	100
Parahippocampal gyrus	42	97	100	100	100	100
Fusiform gyrus	29	45	97	97	100	100

Table 4

Comparison of the percent of subjects showing activation in one run and two runs for each of the tasks in the battery for the targeted regions. Also shown is the number of activated voxels for one run or two runs, the average p-value for two runs obtained from the FDR and the percent signal change in activated clusters after two combined runs. FDR was applied to correct p-values and threshold functional maps. Clusters were sampled with a spatial extent restriction of 10 voxels in each dimension from the cluster's centroid. Note that one run was sufficient only in the combined visual-motor task to reliably activate targeted areas for all of the subjects.

	% subjects from 1 run	# voxels from 1 run	% subjects from 2 runs	# voxels from 2 runs	avg p- value (* 10^{-5})	% signal change
Verb generation task (q=0.01)						
Inferior frontal, left	58	808±110	97	910±74	8.9±3.3	1.1±0.4
Inferior frontal, right	32	745±152	42	791±135	20.4±8.2	1.0±0.1
Superior temporal, left	58	613±86	81	744±84	19.7±6.0	0.8±0.0
Superior temporal, right	23	565±153	29	648±162	17.0±4.8	0.8±0.1
Visual-Motor task (q=0.01)						
Primary motor, left	100	1232±23	100	1317±4	1.8±1.1	1.6±0.1
Primary motor, right	100	1113±53	100	1268±25	10.6±6.7	1.5±0.1
Supplementary motor	90	1007±59	100	1186±38	5.4±1.0	1.0±0.1
Primary visual, left	100	1235±27	100	1302±11	1.5±0.6	1.8±0.1
Primary visual, right	100	1232±26	100	1285±17	2.1±0.7	1.9±0.1
N-Back task (q=0.01)						
DLPFC left	55	979±100	84	979±67	7.4±2.7	0.9±0.0
DLPFC right	39	792±111	74	950±78	7.4±2.0	0.9±0.1
Emotional pictures task (q=0.05)						
Amygdala, left	13	384±99	48	384±103	185.1 ±73.0	1.0±0.1
Amygdala, right	13	547±131	42	511±86	133.1 ±50.1	1.0±0.1
Hippocampus, left	16	233±84	39	502±73	108.8 ±43.7	0.9±0.1
Hippocampus, right	16	370±186	32	667±114	431.2 ±214.7	0.8±0.1