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Clinical Applications of fMRI: An Adaptation of a Standard Neuropsychological Battery

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CLINICAL APPLICATIONS OF FUNCTIONAL BRAIN MAGNETIC

RESONANCE IMAGING (fMRI): AN ADAPTATION OF A

STANDARD NEUROPSYCHOLOGICAL BATTERY

by

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of a dissertation submitted by

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This dissertation has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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As chair of the candidate's graduate committee, I have read the dissertation of Alina K. Fong in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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ABSTRACT

CLINICAL APPLICATIONS OF FUNCTIONAL BRAIN MAGNETIC RESONANCE

IMAGING (fMRI): AN ADAPTATION OF A STANDARD

NEUROPSYCHOLOGICAL BATTERY

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Doctor of Philosophy

The goal of this study is to advance the utility of functional brain imaging as a tool for the diagnosis and treatment of neurological disorders by creating a statistical database of functional MRI (fMRI) brain activation patterns collected from neurologically and psychiatrically unimpaired subjects. Continuous fMRI scans have been obtained from each subject while s/he performed a variety of cognitive tasks that are commonly found in standard neurological and cognitive assessment batteries. The collected fMRI data has been processed, analyzed, and converted into a database which can be used as a reference of reliable indices of normal brain activity patterns for a wide range of cognitive functions.

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

page

LIST OF TABLES

LIST OF FIGURES

page

Clinical Applications of Functional Brain Magnetic Resonance Imaging (fMRI): An

adaptation of a standard neuropsychological battery

Rapid developments in functional magnetic resonance imaging (fMRI)

technology have lead to promising new applications for the diagnosis and treatment of

brain pathology. In contrast to standard MRI, which produces only a static image of brain

structure, functional MRI measures small changes in oxygen flow that occur throughout

the brain as neurons fluctuate in activity levels. Thus, functional MRI allows one to view

areas of the brain that become active, in real time, as individuals engage in mental

activities. Because of its high sensitivity to subtle brain activity, fMRI has shown great

potential in clinical settings as a novel method to evaluate brain function, obtaining data

otherwise unavailable from standard MRI scan procedures.

There are, however, several factors that currently limit the full usefulness of

fMRI, both in clinical and research settings. One problem is the absence of large-scale

normative data sets, or probabilistic activation maps, which would allow quantitative

evaluations of patient fMRI activation patterns for any given cognitive process, with

respect to the unimpaired population that the patient comes from. Without well structured

normative data-bases that reliably and accurately characterize normal brain activation

patterns, it is currently not possible to provide clear, quantitative assessments of

individual patient outcomes that are expressed in terms of statistical deviation from what

would be expected in the absence of pathology. The objective of this study, therefore,

was to begin to build a database of brain images, starting with young to middle-aged

adults. It is expected that in due time, normative data will be collected for younger and

older age groups, respectively.

For this study, brain functioning was examined by means of functional imaging (fMRI). Each participant underwent a series of six fMRI scanning sessions. In each session, continuous fMRI scans covering the whole brain were collected while the participant was engaged in one of six tasks. The six tasks that each participant performed were versions of standard neuropsychological assessments, which have been adapted for use in an MRI scanning environment. These tests included evaluations of memory, language, fluid reasoning, object recognition, and executive functioning. These tests required participants to view images of letters, numbers, shapes, words, and common objects, and to perform simple mental operations, such as memorization, recognition, matching, and problem solving.

Description of Neuropsychological Tasks for Experiments 1-6, and the Respective, Relevant fMRI findings

The body of literature on neuroimaging of cognitive functions which has been produced over the last decade is vast. However, I have limited my literature review to those select studies which I have determined to be relevant approximations of the designs of the six neuropsychological tasks.   With the exception of TMTB, there are currently no studies which consider the approximation of neuropsychology tasks a primary goal. However, there are several studies which are similar, in some respects, to standard neurological tests that I examined in this dissertation, and therefore qualify to serve as suitable comparisons studies for my findings. My discussion and background literature will therefore be limited to studies of this nature.

Matrix Reasoning.

Description.

Raven's Progressive Matrices is commonly accepted as the classic test of inductive non-verbal reasoning in the visual modality (Alderton & Larson, 1990). This test has been generally used to measure and assess abstract problem-solving ability, as responses require neither verbalization, skilled manipulative ability, or subtle differentiation of visuospatial information (Spreen & Strauss, 1998). Both the physical appearance of the test stimuli and the nature of the responses required from the subject make an fMRI adaptation of the standard RPM test fairly straightforward. Each test stimulus consists of a 3 X 3 matrix of figures, with a piece missing. Participants were instructed to deduce what the missing figure should be, and then select it from among the four choice alternatives presented on the right side of the matrix.

Relevant fMRI findings.

Although many imaging studies (i.e. PET, CT, EEG, etc) have researched elements of memory, attention, concentration, learning, and other cognitive functions, relevant fMRI research specifically examining Matrix-type tasks is less available due to its relative nascence. For Raven's Progressive Matrices Test, only two fMRI studies have approximated the task to a reasonable degree. Both studies have elicited activation in the bilateral inferior frontal gyri, medial frontal gyri, the anterior cingulate gyri, and the anterior dorsolateral prefrontal cortex, as well as supplementary motor areas (Christoff, K. et al, 2001, Kroger, et al, 2002).

Trail Making Test.

Description.

The ability to switch between cognitive categories, or "sets," is a classical indicator of normal neurological functioning. The Trail Making Test (TMT) is widely used as a diagnostic tool for eliciting shifts between cognitive sets, or "switching," as well as evaluating cognitive processing speed, attention, sequencing, mental flexibility, and visual search and scanning. The TMT consists of two parts in which subjects must connect 25 circles containing numbers (Part A), or numbers and letters (Part B) arrayed pseudorandomly on a letter-sized sheet of paper. In Part A, the circles are numbered form 1 to 25, whereas in Part B they contain numbers from 1 to 13, and letters from A to L, which must be connected in alternating progression, from 1-A to L-13. Total score is the time in seconds it takes to complete each part and the number of errors incurred through the process. At each error, the administrator must stop and correct the subject before he is able to proceed. In standard test batteries, TMTB is of significantly more importance than TMTA, which is often overlooked, due to the inherent switching requirement of the task (Pontius & Yudowitz, 1980).

Relevant fMRI findings.

To date, two fMRI studies have been reported that involve this classic switching task (Moll, J. et al, 2002, and Zakanis, K. et al, 2005). Zakanis and colleagues used a virtual stylus, which allowed the subject to translate movements across an acrylic tablet. This tablet allowed the subject to link empty circles in random order, using a different random pattern of numbers and letters in each block of the task design. These studies found similar activation patterns, with bilateral parietal cortex, left dorsolateral prefrontal cortex, medial frontal cortex, the associating premotor cortex, and bilateral parietal cingulated sulci activation.

Face Recognition Test.

Description.

The purpose of this test is to assess the ability to recognize familiar and unfamiliar human faces. Alternative versions of this test are currently being administered in the Wechsler Memory Scales-III, the Warrington Facial Recognition Test, and the Test of Memory and Learning. The general form of these exams requires the subject to view a set of faces, under the instructions that they will have to remember the faces at a later time. After a 20-minute delay, the subject is asked to discriminate photographs of faces that were previously seen from unfamiliar novel faces by answering "yes" if the face is one that was seen before, or "no" if it was not.

Relevant fMRI findings.

To date, only a few imaging studies have been conducted that approximate the classic design of the Facial Recognition Test by Benton and Van Allen (1968). These researchers have found significant activation in the left ventral posterior cortex, the anterior- and ventro-occipitotemporal cortices, and the frontal parietal cortex.

Picture Naming.

Description.

Due to the high occurrence of naming difficulties in aphasia and other neuropathological incidences, many neuropsychological screenings contain a naming task (Spreen & Strauss, 1998). Perhaps the most widely use object naming task is the Boston Naming Test, which assesses the subject's ability to name common objects (confrontational naming). In a typical picture-naming task, subjects are shown a series of pictures (e.g., line drawings), and the task is simply to produce a name for each picture.

In the Boston Naming Test, for example, sixty line drawings, ranging from simple, common objects ("chair") to less common objects ("abacus") are presented, one at a time. The subject is to spontaneously produce the name of each object.

Relevant fMRI findings.

Picture recognition and naming have been extensively researched from the very earliest imaging studies. Kanwisher et al (1997), Simons et al (2003), and Kan and Thompson-Schill (2004), have conducted the seminal fMRI studies to date and have successfully approximated an adaptation Boston's classic aphasia examination. Their cumulative findings conclude that the most robust and reliable areas of activation include the fusiform cortex and the lateral occipital cortex (LOC). These areas correspond to the visual object recognition component of the task. Additional reliable areas of activation include the left inferior frontal gyrus (LIFG), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate (AC). These areas correspond to the verbal linguistic component of the task that is involved in the retrieval and articulation of the object.

Verbal Fluency Test.

Description.

The purpose of a verbal fluency test is to evaluate a patient's ability to spontaneously generate words from a specified category within a limited amount of time. The most common versions of this test use either letters of the alphabet or semantic categories (such as animals or fruits and vegetables) as word generation prompts. Letters that are typically used are F, A, S, C, L, P, R, and W. The standard time limit for an test of this type is 60 seconds. Lezak (1995) reports that this task is also useful in assessing

abstract reasoning and problem solving. Additionally, Crockett (1996), reports that this task is sensitive to sequencing, attention, and perseveration.

Relevant fMRI findings.

Although many imaging studies have been reported involving verbal fluency task, only two studies of fMRI experiments, to date, have successfully approximated the design of this task. These two studies conclude that the most reliable areas of activation include LIFG, AC, left temporal lobe, particularly the posterior portion, including the temporal/occipital/parietal junction (TOP) (Abrahams et al, 2003, Gabrieli et al 1998).

Verbal Working Memory.

Description.

Many neuropsychologists give word list learning tasks as measures of verbal memory. The most common word list learning tests are the Rey Auditory Verbal Learning Test and the California Verbal Learning Test. In these tasks, the subject is presented with a list of 16 words, each presented at the rate of 1.5 seconds per word. The subject is then asked to recall as many words as possible, in any order. This process is repeated five times, with the subject optimally able to repeat all 16 words at the end of the fifth trial. Along with the assessment of the strategies and processes involved in learning and remembering verbal material, Spreen and Strauss (1998) report that this test is also useful for evaluating the following cognitive processing constructs:

1. Semantic and serial learning strategies

2. Recall consistency across trials

3. Degree of vulnerability to interference

4. Perseveration

This test is becoming increasingly popular due to its ability to assess multiple aspects of how verbal learning occurs as well as the amount of verbal material learned (Delis et al, 1987).

Relevant fMRI findings.

Although many imaging studies involving verbal memory have been conducted, only two fMRI experiments have been able to approximate the design of the classic verbal memory tests, such as the CVLT and the RAVLT. These previous fMRI studies have elicited robust activations in large, extensive areas of the DLPFC, bilaterally, as well as bilateral ventral prefrontal cortical activation (i.e. Broca's area). These extensive portions of DLPFC and superior left parietal areas are commonly engaged in more difficult, effortful tasks. The left ventral prefrontal cortical areas are engaged as the subject "talks" to him/herself silently throughout the task. The LIFG, premotor cortex, supplementary motor areas are also reliably activated for this task. (Henson et al., Gabrieli et al 1996).

Gender Differences

When evaluating patterns of activation from fMRI studies, it may be important to consider sex differences. Concern about sex differences in the interpretation of neuro-imaging originates largely from observations of sex differences in cognitive performance, where, all things being equal, women tend to outperform men in many aspects of verbal processing, whereas men appear to outperform women in many aspects of spatial processing (Hiscock et al. 1994; Halpern, 1992, 2000; Bryden, 1979; Harris, 1978; McGlone, 1980). One of the dominant questions surrounding current theories of sex-related differences in neuro-cognitive processing is the extent to which such differences

might be attributed to gross differences in brain lateralization and hemispheric specialization across the sexes. This possibility is hard to ignore, given that many reliable sources of evidence over the last several decades suggest that at least some aspects of language processing are carried out in both hemispheres in women, but only in the left hemisphere in men, whereas at least some aspects of spatial processing are carried out bilaterally in men, but only in the right hemisphere in women (Voyer, 1996) Evidence of this sort has lead to various forms of a fairly popular longstanding theory of sex differences in which it is assumed that bilateral processing affords superior cognitive performance (Levi, 1972; Buffery & Gray, 1972).

Previously, evidence for laterality differences between the sexes has come from studies of patients with brain damage (e.g., aphasia), as well as from dichotic listening tasks and split visual field experiments in neurologically healthy subjects (for reviews, see Hyde & Linn, 1988; Voyer, 1996). The reliability of this large body of evidence was recently summarized and evaluated in a rigorous meta-analysis by Voyer (1996). Voyer's analysis includes the results of 396 independent studies from peer-reviewed journals that measured cognitive performance as a function of sex and hemispheric distribution. The results of his study suggest large variation in the reliability of hemispheric-by-sex differences, depending on the specific nature of the "linguistic" or "spatial" task. For example, bilateral processing for lexical decision tasks in women was found to be highly reliable across studies, whereas a bilateral processing advantage for mental rotation in men proved to be much less reliable.

One important issue that Voyer points out however, is the potential bias of the so-called "file drawer problem" in meta-analysis, in which studies with null-results are very

likely to be underreported in the literature (Rosenthal, 1979; Dickersin & Min, 1993). Nevertheless, Voyer's analysis reveals reliable trends that are hard to ignore. One trend that stands out as being particularly robust is a bilateral advantage for women in language comprehension (including lexical decision, naming, and object-word matching), which was significantly stronger for stimuli presented in the visual modality.

fMRI offers a fairly straightforward way to explore sex differences in cognitive processing, with respect to laterality issues, as well as other neurologically-defined distinctions. Recent functional neuroimaging studies have examined most of the verbal processing subtypes that were identified by Voyer as most likely to involve bilateral processing in women. Although many of these studies support the notion of a bilateral verbal processing advantage for women (Shaywitz et al., 1995; Pugh et al., 1996; Jaeger et al., 1998; Kansaku et al., 2000; Phillips et al., 2001; Rossell et al., 2002; Baxter et al., 2003; Gur et al; 2000; Goldstein et al., 2005), others do not (Frost et al., 1999; Schlösser et al., 1998; Buckner et al., 1995; Price et al., 1996). Moreover, it is reasonable to assume that a bias against null-result reporting is just as much a factor in the fMRI literature as it is elsewhere.

In terms of positive findings, the most reliable fMRI evidence for a bilateral processing advantage in women comes from auditory sentence comprehension studies (e.g., Kansaku et al., 2000; Phillips et al., 2001), in which subjects listen to segments of prose, compared to noise (e.g., backwards speech). Another type of task that appears to elicit reliable effects is one that requires semantic evaluation of individual words, in either auditory or visual modalities (Shaywitz et al., 1995; Pugh et al., 1996; Baxter et al., 2003).

In contrast to these studies, Frost et al. (1999) provides compelling evidence against the notion of a bilateral verbal processing advantage for women. Using an auditory version of the semantic decision design, comparable to that of Pugh et al (1996) above, Frost and colleagues collected data from a much larger sample of subjects (50 men, 50 women) than what is typical in fMRI studies (e.g., samples sizes range from 12-47 in the studies reported above). While some researchers (e.g., Harasty, 2000) have objected that the auditory-based study of Frost et al. cannot be directly compared the visual-based study of Pugh et al., further arguments by Binder, Frost, et al. (2000) point out that other fMRI studies using visual stimuli in experimental designs similar to that of Pugh et al.(1996) have revealed null-results as well (e.g., Price et al., 1996).

To summarize, the general pattern of findings across the studies reviewed here suggests that if sex-based differences in language performance are, in fact, attributable to differences in hemispheric specialization, the contributions of this factor appear to vary widely across different sub-types of language processing. One aspect of language processing that has not been examined in fMRI studies with respect to sex differences is object naming. As there were very few studies available at that time for Voyer's meta-analysis that employed the tasks that are examined here, his (1996) meta-analysis does not lead to any obvious predictions as to what we may expect in these experiments.

General Hypothesis

My hypothesis is that my findings are consistent with those of previous, relevant fMRI brain activation patterns for each of the six tasks, enabling the assembly of a database around fMRI findings. A second hypothesis is that my findings are consistent with the hypothetical neural systems traditionally implicated in the standard, paper and

pencil tasks. I view this project as a critical step toward making fMRI a reliable

instrument, not only for the benefit of clinical diagnosis, but also for the advancement of

basic empirical research in the brain and behavioral sciences. Furthermore, I have clear

expectations and predictions about the form our data should take, as stated in the previous

section, which will allow us to evaluate the success of the project. Following the

hypotheses, the objectives are as follows: 1) determine what brain areas are engaged for

each of these fMRI adapted tasks, 2) assess the reliability of the activations for these

tasks, and 3) create an index of the reliability of each task for use in more clinical,

diagnostic settings.

Task-specific hypotheses.

Specific predictions of activation for each task are as follows. For each

experiment, the key areas of predicted activation are listed below and numerically co-

indexed with a corresponding diagram superimposed on the Montreal Neurological

Institute (MNI) statistically averaged brain, which is a composite of 305 individual

brains.

Matrix Reasoning. See Figure 1.

1. Bilateral inferior lateral occipital, and inferior middle lateral
    occipital, both stronger on the right.

2. Bilateral fusimform gyrus.

3. Bilateral thalamus (including inferior and superior thalamus).

4. (a)Bilateral frontal operculum (including the basal ganglia,
    bilaterally), (b)the dorsal processing stream, which extends
    dorsolaterally from the primary visual areas in the occipital cortex.

5. Superior parietal lobule (SPL), including the inferior parietal sulci (IPS). Although this activation was bilateral, it was stronger on the right than the left.

6. Dorsal anterior cingulate and bilateral medial supplementary motor areas (SMA), although it was stronger on the left.

7. Bilateral precentral gyrus activation, although it was stronger on the left, medial frontal gyrus activation only on the right.

8. Anterior middle frontal gyrus activation only on the left.

9. Fronto-polar activation on the right.

10. Tip of the superior frontal gyrus on the left.

Figure 1.
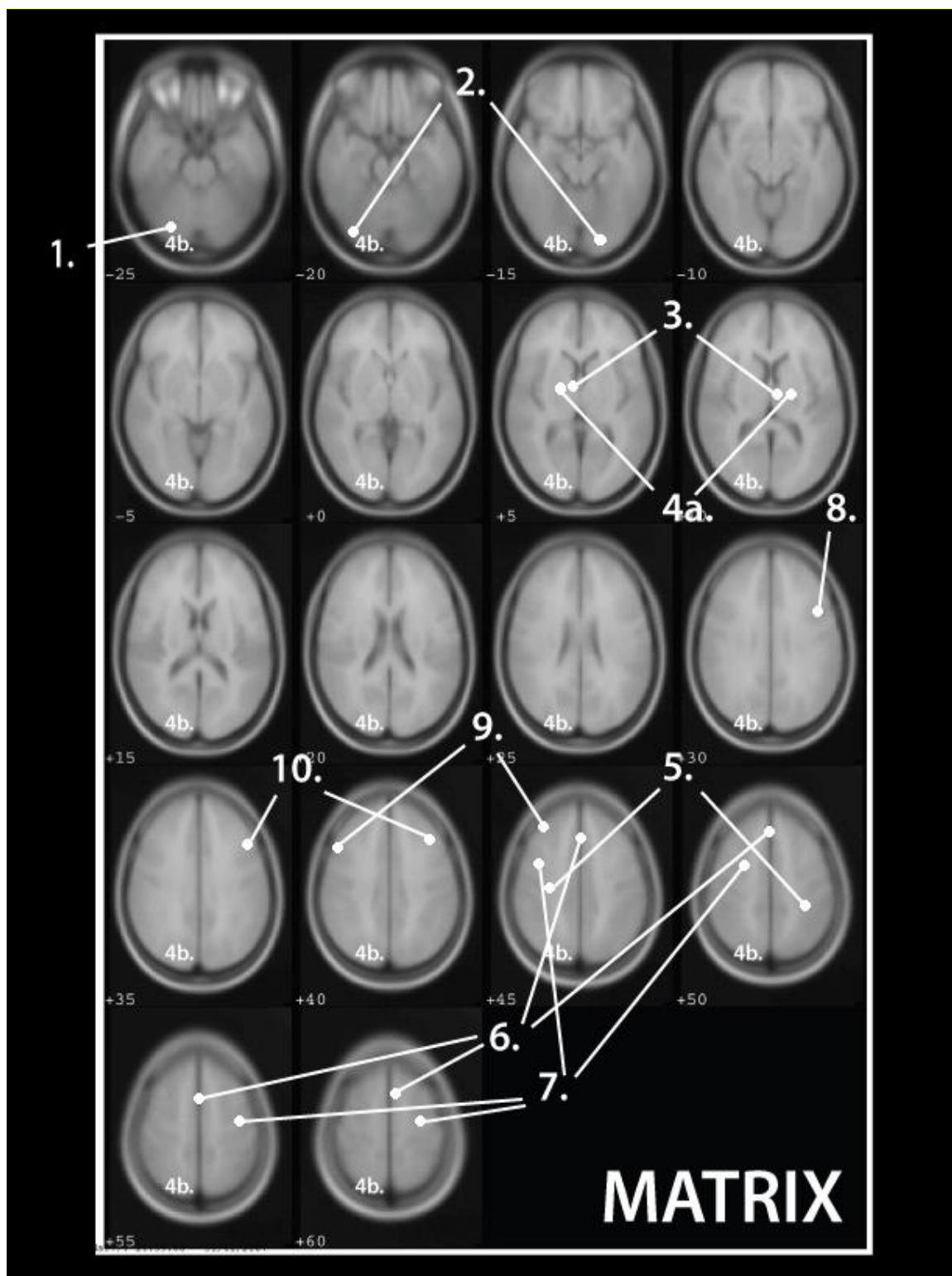
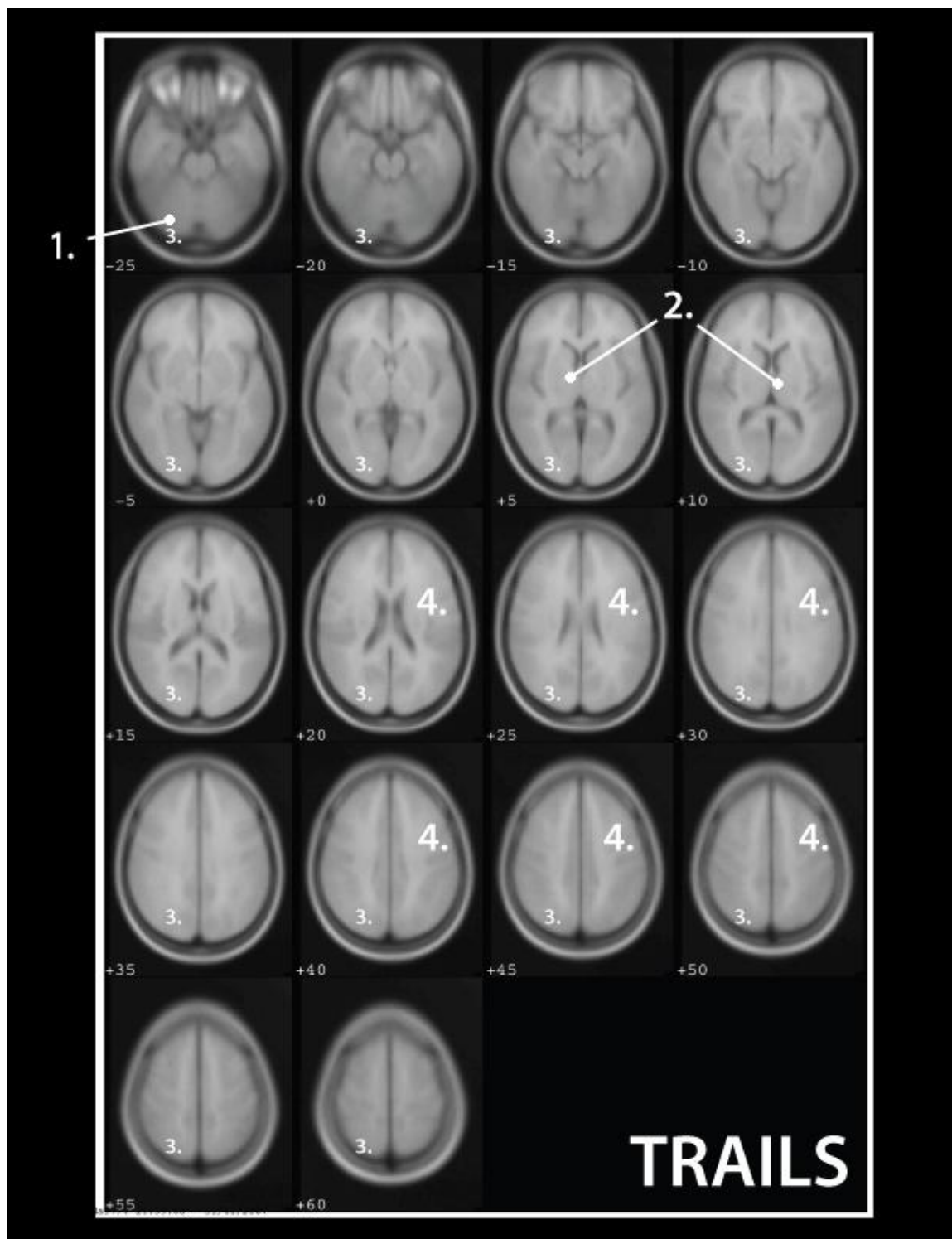*Trail Making Test*. See Figure 2.

      1. Bilateral fusiform, with stronger activation on the left.

      2. Inferior thalamus, bilaterally.

      3. Dorsal processing stream from the LOC to the superior parietal lobule, including the IPS, bilaterally, but with a little stronger extension into the IPS on the left.

      4. Left precentral motor cortex, and the left medial SMA.

Figure 2.

Picture Naming Test. See Figure 3.

> 1. Bilateral fusiform activation, but much stronger on the right.
>
> 2. Small dorsal processing stream activation, bilaterally.
>
> 3. At lower thresholds, mean activation included areas which one would typically expect for a Picture Naming task, including strong left frontal operculum (Broca's area), and left speech motor areas.
>
> 4. Bilateral anterior cingulate.
>
> 5. Left thalamus activation.

Figure 3.

P NAMING
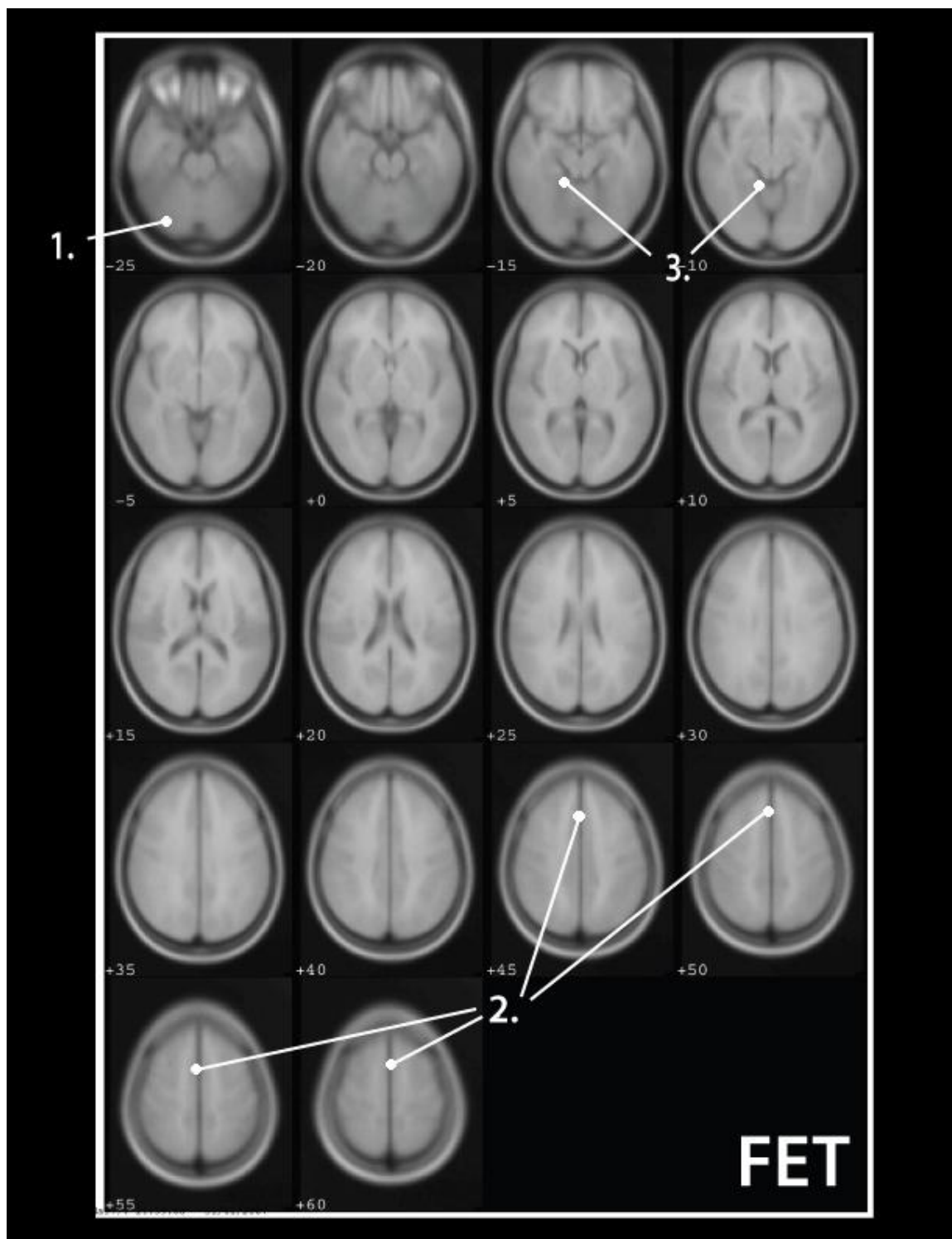
Face Recognition Test. See Figure 4.

   1. Bilateral fusiform and LOC, but with much stronger activation on the

    right.

   2. SMA bilaterally, with stronger activation in the right precentral motor

    cortex, the left caudate (superior portion).

   3. Right posterior hippocampal, medial hippocampal, and parahippocampal

    gyral activation.

Figure 4.

Verbal Memory Test. See Figure 5.

      1. SMA bilaterally.

      2. Medial frontal gyrus (MFG).

      3. Left in the speech motor areas.

      4. Thalamus.

      5. IPS.

      6. Fusiform gyrus.

      7. Primary visual cortex (V1).

      8. There was also some activation on the right inferior LOC.

Figure 5.
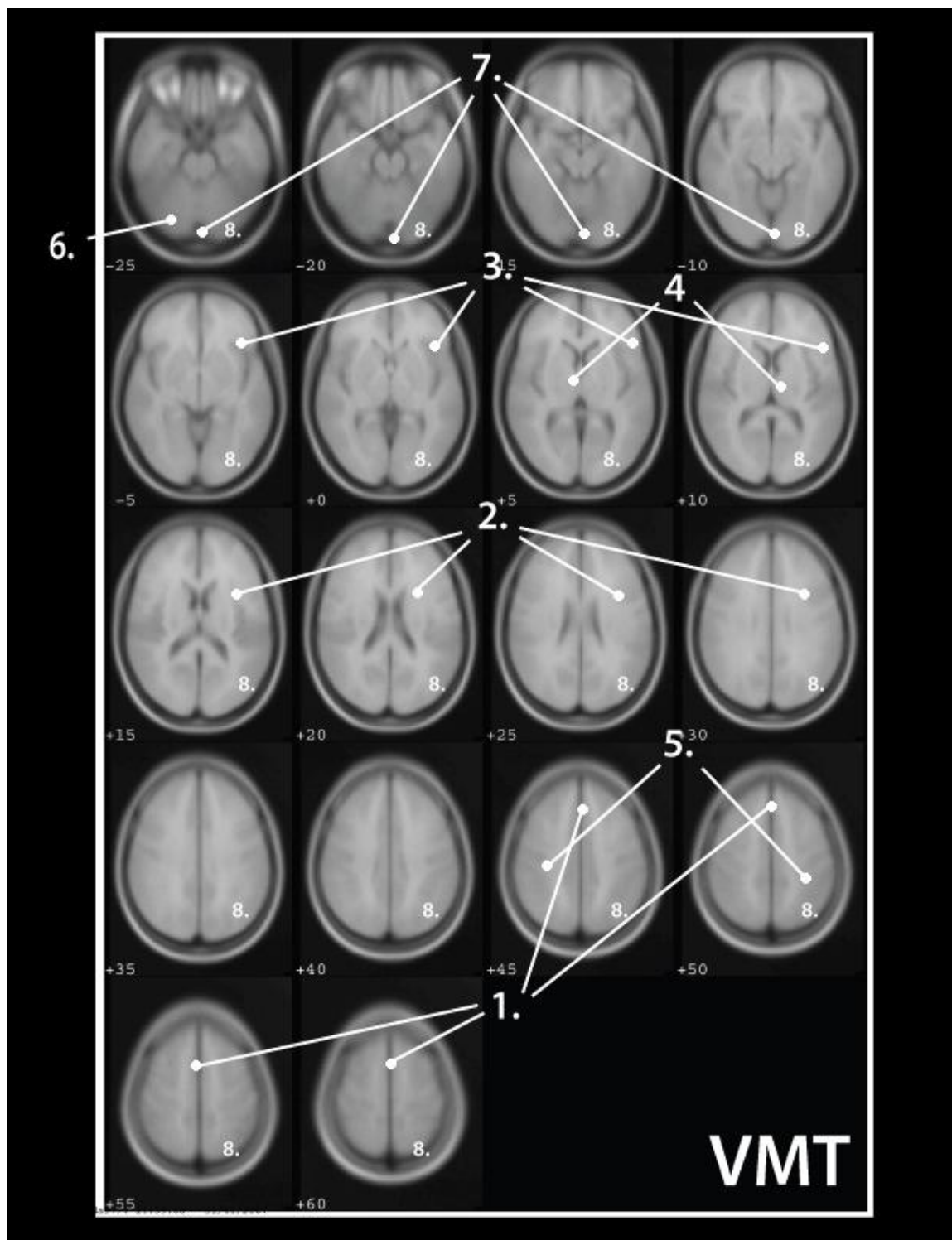
Verbal Fluency Test. See Figure 6.

      1. Left caudate and left frontal operculum.

      2. Broca's area (left inferior frontal gyrus which extends to Broca's area).

      3. The speech motor cortex, and bilateral SMA.

      4. Also, out of all the six tasks, this task elicited the greater amount of AC

         activity. Also, there was no noted activation in visual areas.

Figure 6.

Method

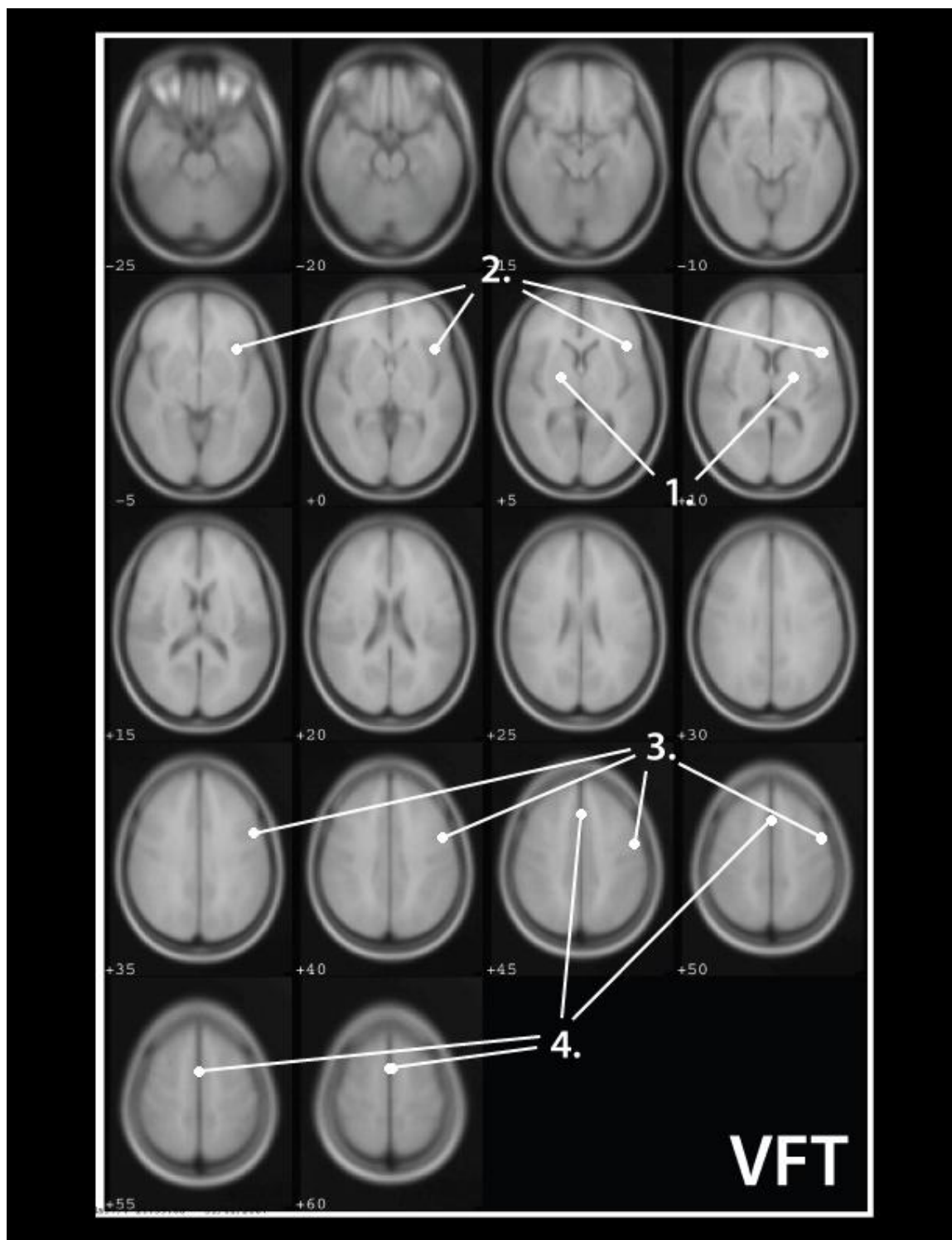*An Introductory Overview of Special Issues Relating to Data Collection, Processing, and Statistical Analysis in fMRI Research*

This preface to the Methods section of my dissertation is a brief primer on important technical points that are particular to fMRI research. It is intended as a supplement for readers with no previous background in functional imaging methods. Readers already familiar with fMRI research, and with the SPM software approach in particular, may wish to skip directly to the Methods section.

Image Acquisition

For all functional MRI scanning, we used a gradient echo, echo-planar imaging (EPI) sequence. This EPI protocol is optimized for detecting subtle changes in blood oxygenation content in the brain over time. Thus EPI scanning is an effective way to measure changes in the so-called *Blood Oxygen Level Dependent* (BOLD) signal, which has been shown to reliably correlate with changes in neural activity (Ogawa, Lee, Kay, & Tank, 1990). In all of the experiments for this study, we used an EPI sequence with a field of view covering the entire brain, which enabled us to continuously monitor BOLD signal intensity changes from the whole brain throughout the duration of each scanning session.

During scanning, BOLD signal intensity samples were taken by means of 23 contiguous horizontal (axial) slices, acquired in a bottom-up, interleaved fashion. Each axial slice was 5mm thick and included a 64x64 matrix of individual sample points, with each sample point covering a $3.75x3.75mm^2$ section of the slice. Thus, the entire brain

was sampled with total of 64x64x23 (94,208) *voxels* (i.e., three-dimensional pixels), at a

resolution of 3.75x3.75x5mm for each voxel. As the EPI sequence requires 2 seconds to

acquire each whole brain image, the BOLD signal from each voxel was sampled every 2

seconds (See Figure 7).

Figure 7: Placement of 23 axial slices. Each slice includes a 64x64 matrix of voxel sample points.
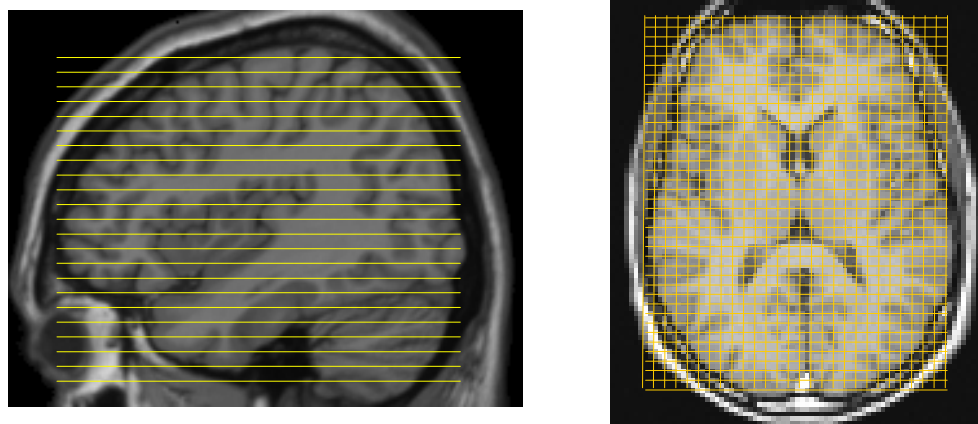
Task Design

Timing of the BOLD Signal. Recent research into the physiological processes that

give rise to the BOLD effect, as well as its relationship to neural activity (see for recent

reviews, Faro & Mohamed, 2006; Huettel, Song, & McCarthy, 2004), has provided

researchers with several convenient guidelines for designing fMRI experiments in a way

that optimizes the likelihood of revealing the neural systems that underlie cognitive

processes of interest. A good understanding of the basic temporal properties of the BOLD

effect, in particular, is especially important in both the design and the statistical analysis

of fMRI experiments.

The temporal course of the BOLD signal is best understood in terms of the

Hemodynamic Response Function (HRF). When neurons begin to fire vigorously,

through a process that is not entirely understood, the capillaries that supply those neurons expand, allowing more oxygen-rich blood to flow into the region of the active neurons. This *hemodynamic response* to neural activity has certain temporal properties that are fairly consistent throughout the brain. Although the net BOLD signal detected by EPI scanning may also be affected, to some degree, by other physiological variables, the dominant contribution of the HRF results in a BOLD time-course with the following general properties (See Figure 8):

1. The BOLD signal begins to rise about 2 seconds after the onset of neural activity (sometimes there is a very slight initial dip in the signal).

2. The signal peaks between 4-6 seconds after the onset of neural activity.

3. The signal returns to baseline around 10 seconds after the onset of neural activity.

4. The signal dips below base-line between about 10-15 seconds post-onset

Figure 8. The HRF effect on the time-course of the BOLD signal.
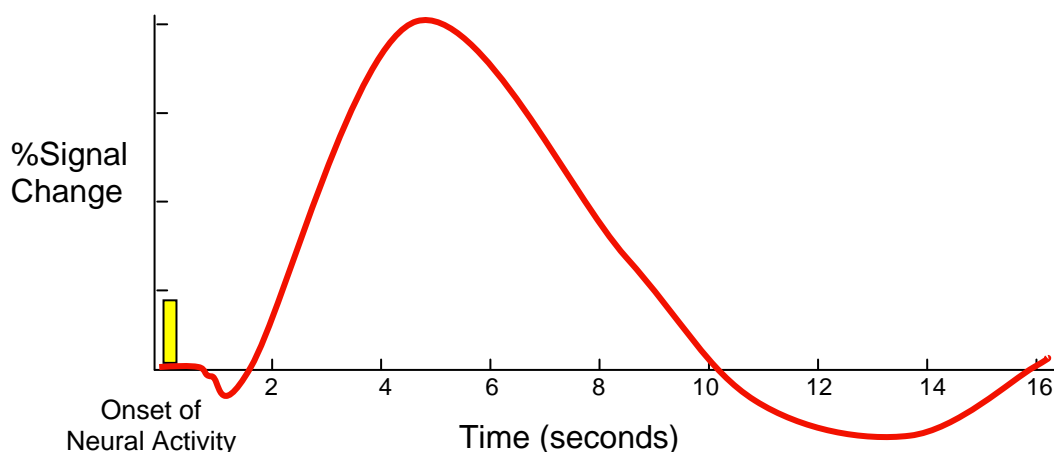
Another important factor to consider regarding the HRF effect is that sustained neural activity will often give rise to a sustained peak of the BOLD signal. So, for example, a cognitive event that happens very quickly (e.g., around 200ms), such as the recognition of a printed letter in the visual cortex, will likely give rise to a BOLD signal similar to that in Figure 8. However, a cognitive event of a more sustained nature, such as verbal rehearsal, or complex problem solving, will likely result in a sustained bold signal peak, as depicted in Figure 9.

Figure 9. The HRF effect on the time-course of the sustained BOLD signal.
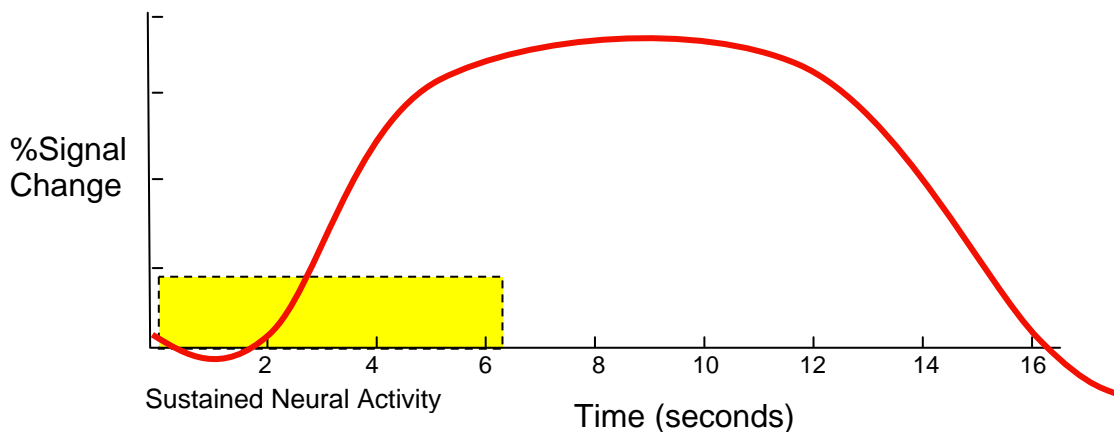
Theoretically, a signal with a sustained peak will be easier to detect statistically than a brief peak, given that the strength and reliability of the BOLD signal is often subject to many other "noisy" variables, such as atypical cardiac and respiratory cycles, random magnetic fluctuations, atypical HRF variations, transient atypical neural firing and/or metabolic processes, atypical neural-HRF coupling, etc. However, it is nonetheless possible to detect brief BOLD signals related to fast cognitive events, provided that the events are repeated many times (e.g., 30 repetitions), and very tight experimental controls are included in the design (see Dale, 1999; Menon, Lucknowsky, & Gati; 1998).

All things being equal, however, fMRI designs that require sustained epochs of cognitive processing (or brief cognitive events, repeated several times in succession) stand a better chance of producing robust and reliable results. Taking into consideration such things as typical cardiac and respiratory cycles, typical HRF shapes, and EPI sampling limitations, Huettel et al. (2004) suggest that the optimal fMRI design is one that includes about 6-8 cycles of epochs (or *blocks*) in which the subject engages in a cognitive activity of interest for about 12-18 seconds, followed by a rest period, or a period of alternative cognitive activity, for at least 10 seconds. For sufficient statistical power, 6-8 repetitions of a task/rest cycle appears to be adequate. However, with too many cycles, one runs the risk of subject fatigue, or even worse, HRF attenuation due to habituation effects. Many studies (see especially, Grill-Spector & Malach 2001), have shown that the BOLD signal can decrease dramatically as a subject becomes more efficient at performing a cognitive task, with repeated practice.

Taking the above-mentioned factors into consideration, our basic strategy in designing the fMRI experiments of this study, was to arrange each cognitive activity of interest, for each experiment, in such a way as to maximally engage the subject in a sustained cognitive epoch for 10-18 seconds, followed by a period of rest for about 10-18 seconds. Blocks of task/rest varied from 6-24 cycles. The exact duration of cognitive activity and number of cycles varied for each experiment, depending on the nature of the particular cognitive task involved.

Another important factor of our design concerns the so-called "rest" period. One of the more common approaches in fMRI experiments is to include rest periods in which the subject either does nothing at all, or engages in an entirely non-demanding task, such

as looking at a simple visual stimulus, such as a fixation cross ("+"). One concern, however, is that during a so-called rest period, subjects might not be entirely "resting" in terms of cognitive activity. Most likely, subjects lying in a scanner with nothing to do for several seconds will likely engage in any number of cognitive processes, including covert language, memory, and executive functioning (e.g., day-dreaming, reminiscing, planning future events, pondering urgent problems, etc.). A recent fMRI experiment by Binder et al. (1999) looked specifically at cortical activity during a typical resting phase. They found that subjects tend to heavily engage the language and executive planning areas of the left inferior frontal cortex.

A further concern, however, is that one may never know exactly what any individual may choose to do during the rest period. A solution to this potential loss of experimental control during the resting state, suggested by Stark and his colleagues (Stark & Squire, 2001), is to use a task that is minimally cognitively demanding, yet provides subjects with a controlled activity. The task that Stark and colleagues suggest is to simply have subjects count by ones (covertly) throughout the rest period. Because this alternative task has been shown to only very weakly engage language areas of the cortex, and because it effectively prevents subjects from engaging in other random cognitive activities, we use a simple counting task for the rest period activity in our experiments.

Relation of Task Design to Statistical Analysis

The basic statistical approach that we use is a time-series variant of the ANCOVA (Analysis of Covariance) form of the General Linear Model. Put in simplest terms, this statistical approach tests each voxel in the brain, for each subject, against the null-hypothesis that over the duration of the experiment the rise and fall of the BOLD signal

coming from that voxel does not significantly correlate with the onsets and offsets,

respectively, of the cycles of cognitive task of interest.

In order to carry out the voxel-by-voxel statistical analysis, a weighted model is

created that starts with a simple model of the on-off timings of the events of interest. This

is the so-called "box-car" design. For a design with only one task variable of interest, for

example, a simple face memorization (FM) task carried out for 16 seconds per cycle, with

an alternating "rest" counting task (CT) epoch of 12 seconds per cycle, the box-car

weighting input to the model would be as depicted in Figure 10.

Figure 10. "Box-Car" input weights for a face-memorization task

... x 8 cycles

FM 16 s   CT 12 s   FM 16 s   CT 12
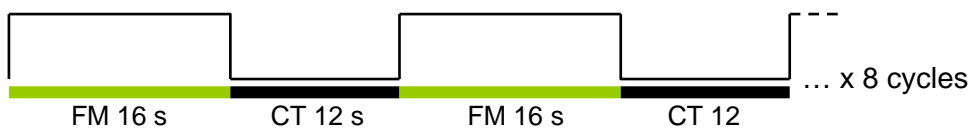
In Figure 10, the on-periods are simply given a weight of one and the off-periods

a weight of 0. However, in reality we do not expect the BOLD signal to follow these

ideal on-off properties. Instead, we expect that the BOLD signal will follow the

properties of the HRF (e.g., Figure 11). In order to accommodate a more physiologically

realistic expectation, the box-car weights are *convolved* with a generic HRF wave-form

model (a composite of two synthetic gamma functions), to yield a parametric model of

continuous weight values for the task variable.

Figure 11. Box-car weights are convolved with idealized HRF shape; (X) = convolution operator
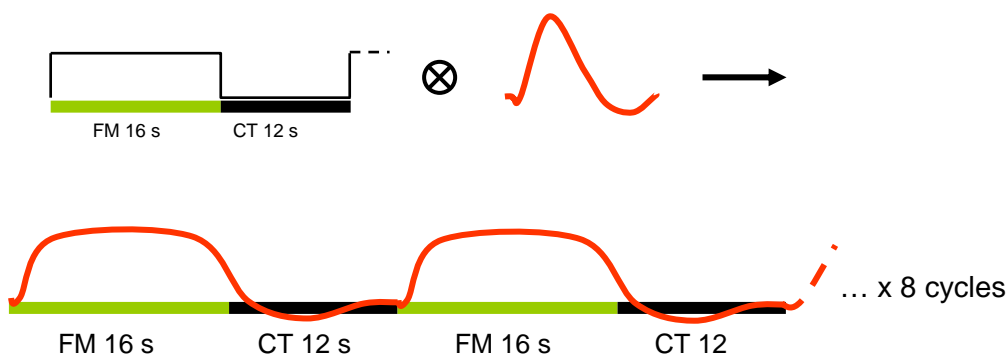
One benefit of using the ANCOVA model, is that it allows one to include any number of regressors to model nuisance variables. In our analyses, we include only one such regressor, which models the global signal intensity of the whole brain. During an fMRI session, random fluctuations of BOLD signal strength will invariably arise from such things as natural respiratory cycles, cardiac flow cycles, transient changes in magnetic field properties, and other factors. These random signal fluctuations tend occur across the whole brain and are often of a much greater magnitude than the more local changes that might arise at the voxel-level from the effects of experimental manipulations on neural activity. Given these factors, it is highly recommended that one include a continuous model of the average signal across the whole brain, as a regressor of no-interest, in the ANCOVA design. An example of the complete ANCOVA model for a single subject with one covariate (Face Memory) and one regressor (Global Signal) is shown in Figure 12 below. This figure, referred to as a *design matrix*, was generated by the SPM fMRI analysis software that we use. The FM covariate is represented by the left column, and the Global regressor is on the right. Time is represented on the y-axis, in a top-down fashion. Weight strength, at each time point, is represented in terms of grey-

level brightness, with the strongest positive weighting represented as the brightest white, and the lowest (negative) weighting as darkest black (e.g., for the task covariate in the left column, imagine looking down onto the tops of the HRF curves, as in Figure 12, with the tops of the curves being the whitest points).

Figure 12. Full ANCOVA model (Design Matrix) for a single subject
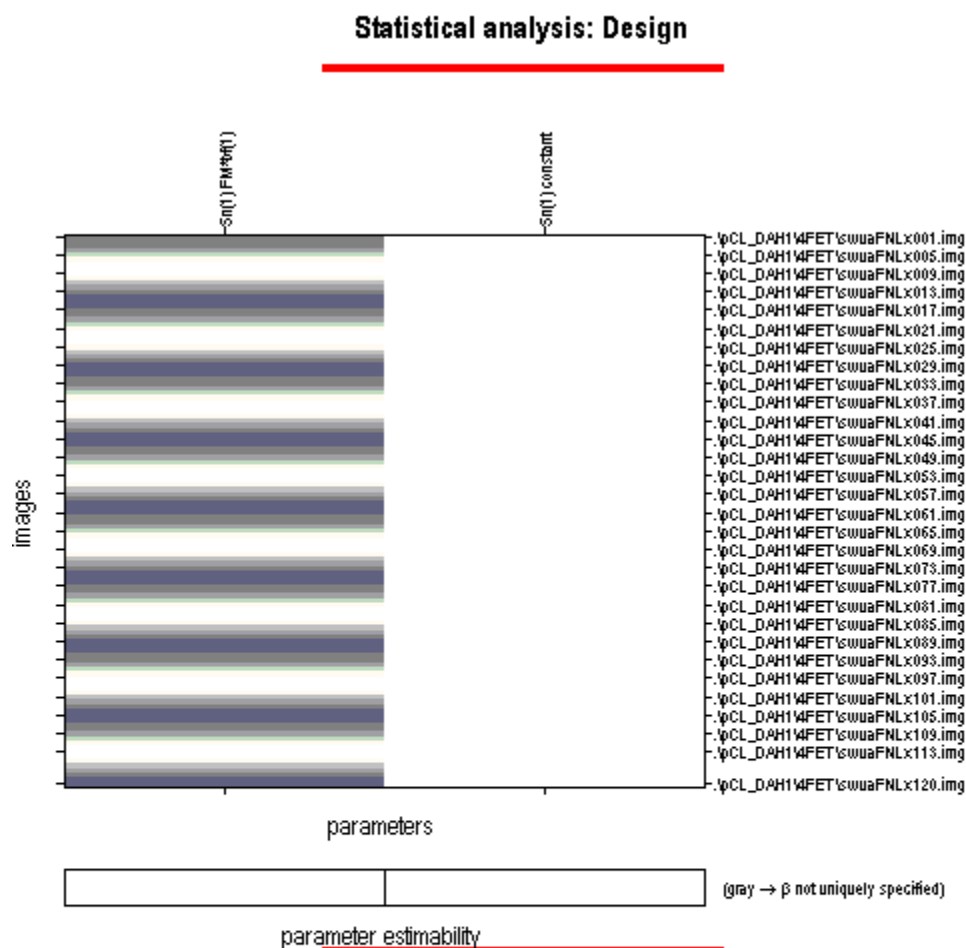
Single-Subject to Group Analyses, Probability Maps, and Displaying the Results.

The resulting product of the ANCOVA computation on a single-subject's data is a 3-dimensional map of *t*-values. An example of a single-subject's *t*-value map is shown in Figure 13. The magnitude of the *t*-value at each voxel is represented as grey-level brightness, with brighter voxels representing higher *t*-values.

Figure 13. Map of t-values for a single subject.
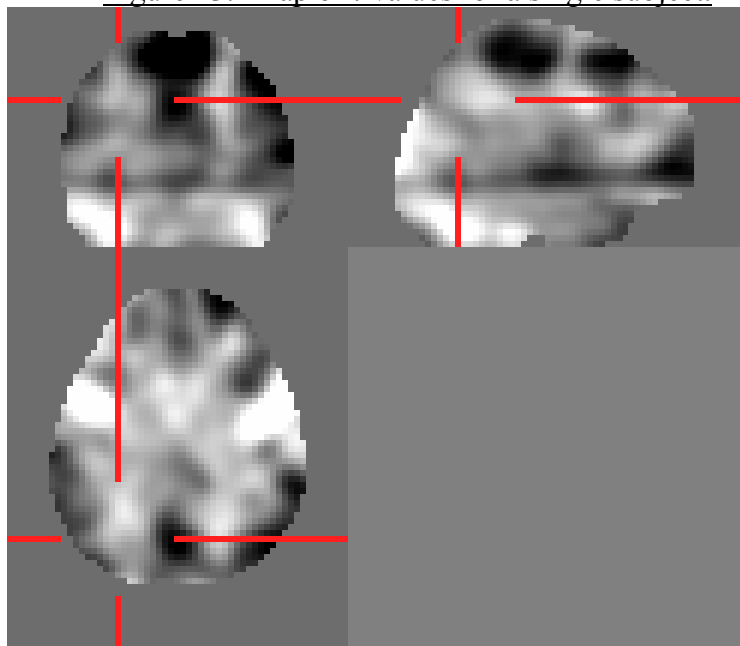
A *t*-value map can then be converted into a *probability* map (a map of corresponding p-values) and the results can be displayed at whatever threshold is desired. (e.g., p < .05). Typically, the results are color-coded, with brighter colors representing lower (more significant) p-values and are overlain on a higher-resolution MRI image, in order to facilitate identification of finer-grained cortical structures (By necessity, EPI images have relatively poor resolution [e.g., $3mm^3$]).

A current issue in fMRI research concerns the most appropriate way to analyze data from more than one subject. The approach that we use is based on a fairly well-

accepted (and statistically conservative) solution suggested by Penny, Holmes, and Friston (2003). The approach is pretty straightforward. The first requirement is that each subject's brain be normalized into a common 3-dimensional stereotactic space before each individual's *t*-map is computed. Then the value of the sum of the contrast weights for each voxel from each subject computed during the ANCOVA (basically, the numerator of the *t*-statistic) is entered as a single data point in a new, "second-level" *t*-statistic computation. In this second-level computation, then, the mean value for each voxel across subjects is modeled as the effect term and the variance between subjects as the error term. In the results sections of this study, the maps shown depict probabilities derived from exactly this type of second-level group-wise *t*-statistic. An important consequence of this approach to keep in mind is that it is very unlikely that a voxel will show significant activation on the group-level map, unless virtually all of the subjects show activation at that voxel. This second level analysis as a random effects approach (RFX) in the results section.

Participants

To be included in this study, participants were between 20 and 40 years old (26 subjects total: 13 male, 13 female) who had no obvious neurological impairments (as screened in the questionnaire). The mean age for all subjects was 25.04, with a standard deviation of 4.23. All but two subjects were determined to be dominantly right-handed with a mean score of 79 on the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects were Caucasian, except for one Asian/Pacific Islander male. All subjects had at least a high-school education. All subjects spoke English as a first language, and 10 of the 26 subjects also spoke a second language acquired in adulthood (See Table 1).

Table 1. Subject Demographics

			FET	Post- Test				Speak 2nd Language	
DATE	Num	Sex	Hit	CR	%Correct	Handedness	Age		Ethnicity
20051020	1	M	5	5	100	Left	23	Y	Caucasian
20051101	2	F	5	5	100	Left	22	N	Caucasian
20060126	3	M	5	5	100	Right	29	Y	Asian
20060201	4	M	5	5	100	Right	24	Y	Caucasian
20060208	5	F	5	5	100	Right	21	N	Caucasian
20060215	6	M	5	5	100	Right	29	Y	Caucasian
20060216	7	F	3	5	80	Right	21	N	Caucasian
20060221	8	F	5	5	100	Right	21	N	Caucasian
20060223	9	M	5	5	100	Right	22	Y	Caucasian
20060302	10	F	5	3	80	Right	25	N	Caucasian
20060314	11	F	5	5	100	Right	23	N	Caucasian
20060323	12	F	4	5	90	Right	25	N	Caucasian
20060328	13	M	4	2	60	Right	26	N	Caucasian
20060415	14	M	5	5	100	Right	25	Y	Caucasian
20060517	15	M	4	5	90	Right	38	Y	Caucasian
20060518	16	M	5	5	100	Right	28	Y	Caucasian
20060525	17	M	5	5	100	Right	26	N	Caucasian
20060607	18	F	5	5	100	Right	22	N	Caucasian
20060608	19	M	4	5	90	Right	29	Y	Caucasian
20060614	20	F	5	5	100	Right	28	N	Caucasian
20060712	21	F	5	5	100	Right	25	Y	Caucasian
20060728	22	F	5	5	100	Right	24	N	Caucasian
20060804	23	M	5	5	100	Right	28	N	Caucasian
20060810	24	M	4	5	90	Right	22	N	Caucasian
20060901	25	F	5	5	100	Right	22	N	Caucasian
20060907	26	F	5	5	100	Right	23	N	Caucasian

Recruitment for this study was non-traditional and deserves some comment. Because data collection and analysis are rather expensive and time consuming in fMRI research, a high level of participant comfort, satisfaction, and compliance is required. In previous experience, people who are already acquainted with our lab and its members (e.g., fellow faculty, student research associates, family, and friends) tend to meet this requirement the best. For this reason, invitations to participate are made informally, under the principle investigator's discretion. A majority of subjects were randomly invited from

a pool of undergraduate introductory psychology courses. This method has been used successfully for similar studies over the last several years both at BYU and elsewhere. Although this study is limited by convenience sampling, there are many variables including gender, age, socioeconomic status, ethnicity, etc. which will require further research in future studies. Prior to scanning, subjects were administered a questionnaire which included basic screening and exclusion criteria prior to being scanned. See Appendix 1 and 2 for screening questionnaire and patient consent form, respectively.

Description of fMRI Protocols

In order to make the data produced in this study relevant to the field of neuropsychology, it was necessary to provide participants with a testing experience that was close enough to what they experience in standard paper and pencil neuropsychological evaluation. However, the MRI scanning environment itself in many ways prohibits exact replications of neuropsychological assessments. One of the major challenges of this study, therefore, was to approximate as closely as possible the standard test battery within several confines and limitations of fMRI without deviating so far from the basic format of the assessment as to render the respective data sets incomparable. However, in order to accommodate the limitations of the MRI environment, certain deviations were necessary and will be described in each task below.

These limitations of MRI scanning environment include:1) the subject is not able to move, 2) there can be no metal in the scanning room, 3) the task needs to be repeated several times, 4) sessions must be fairly short (<5 minutes), or else data files become impossibly large to handle computationally.

Matrix Reasoning

Both the physical appearance of the test stimuli and the nature of the responses required from the subject make an fMRI adaptation of the standard RPM test fairly straightforward. Each test stimulus consists of a 3 X 3 matrix of figures, with a piece missing. Participants are instructed to deduce what the missing figure should be, and then select it from among the four choice alternatives presented on the right side of the matrix (Figure 14).

Figure 14. Sample Matrix stimuli.
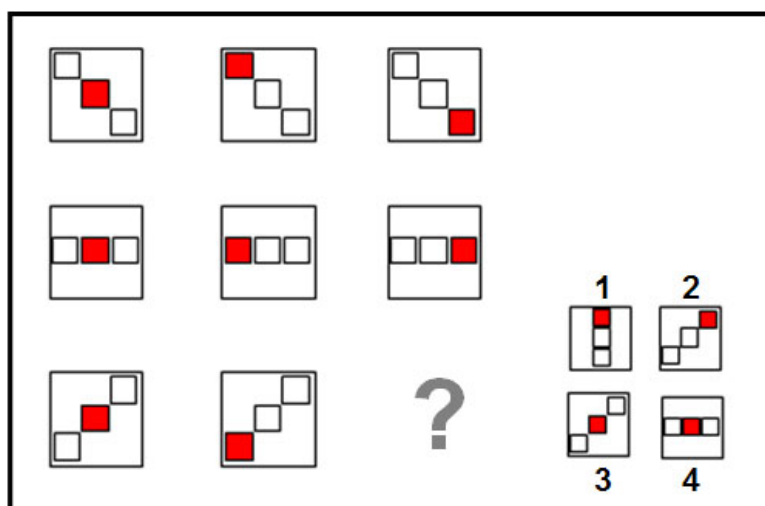
Inferring the correct answer required considering the converging change along both dimensions. Thus, these problems require that two relations be integrated, or considered simultaneously. Once the subject had solved the problem, he pushed a button on a fiber-optic response pad (FORP), which registered the amount of time it took to solve the problem, and advanced the computer to the next problem. Although the accuracy of the subject's responses was not tested, his response times were. The study's interest lies more within the brain functions engaged in trying to solve the problem, rather than

whether the answer is correct or incorrect. This principle applies to all six tasks. See

Table 2 for further description and timing of protocol.

Table 2. Timing of Matrix Reasoning.

Matrix Reasoning
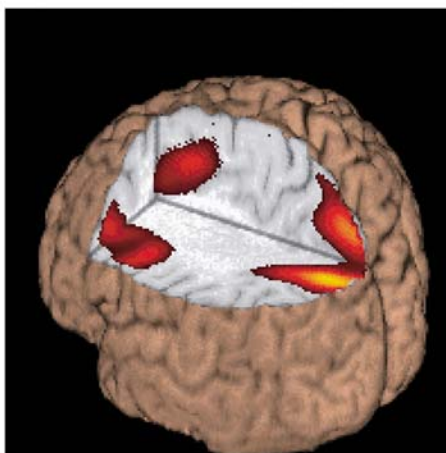
- Most familiar as Raven's Progressive Matrices
- Generally used to assess abstract problem-solving ability
- Requires no verbalization or subtle differentiation of visuospatial information
- Each test stimulus consists of a 3 x 3 matrix of figures with one missing piece
- Subject chooses correct missing figure from four alternatives
- Response choice and latency recorded via fiber optic manual response pad
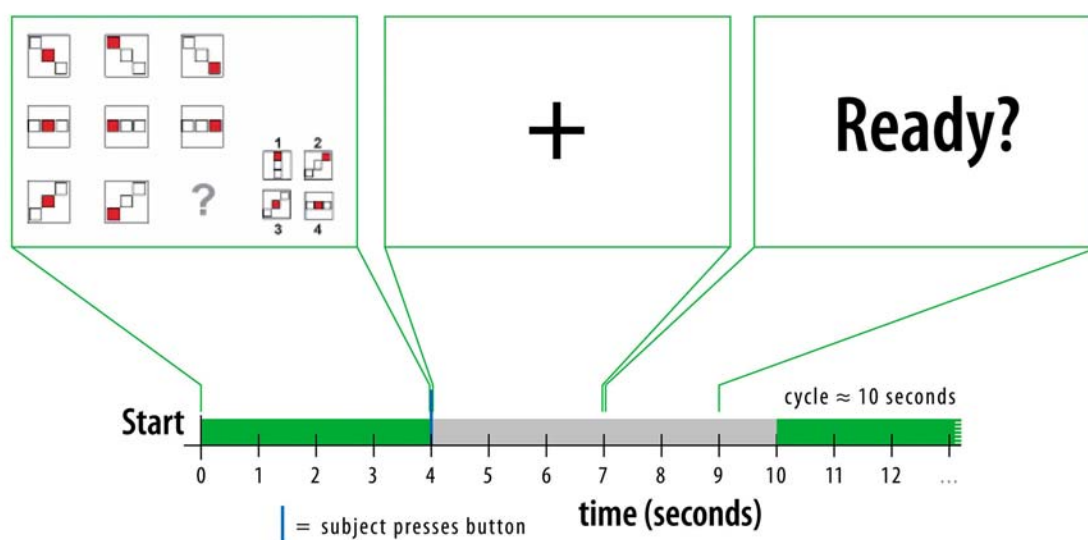
Trail Making Test

As stated previously, between the TMTA and the TMTB, the latter is viewed as the most useful indicator of brain dysfunction, due to its complexity. Therefore, the fMRI adaption of this task included only TMTB. While in the scanner, the subject was presented with a presentation of numbers and letters, with the first number in the sequence circled. As soon as the subject found the next letter in the sequence, s/he pushed a button on a FORP pad, which then highlighted the next circled letter and drew a line connecting the two, thus simulating the paper and pencil test. If the subject were incorrect, this procedure allowed for a visual "correction" before permitting him to proceed. See Table 3 for further description and timing of protocol.

Table 3. Timing of Trail Making Test

Trail Making Test
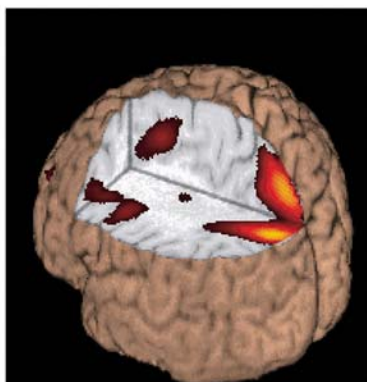
- Modeled after the familiar trail making test (TMT, Part B)
- Used to assess cognitive set shifting, cognitive processing speed, attention, sequencing, mental flexibility, and visual search and scanning.
- The TMT (Part B) consists of 25 circles containing numbers and letters on a letter-sized sheet of paper.
- fMRI adaptation: Subject views TMT array, with the first number in the sequence circled.
- As soon as the subject finds the next letter in the sequence, he or she presses a button
- Each button press highlights the next circled letter and draws a connecting line
- This procedure allows for a visual "correction" before permitting subject to proceed, thus simulating the "feedback" component of the standard TMT administration
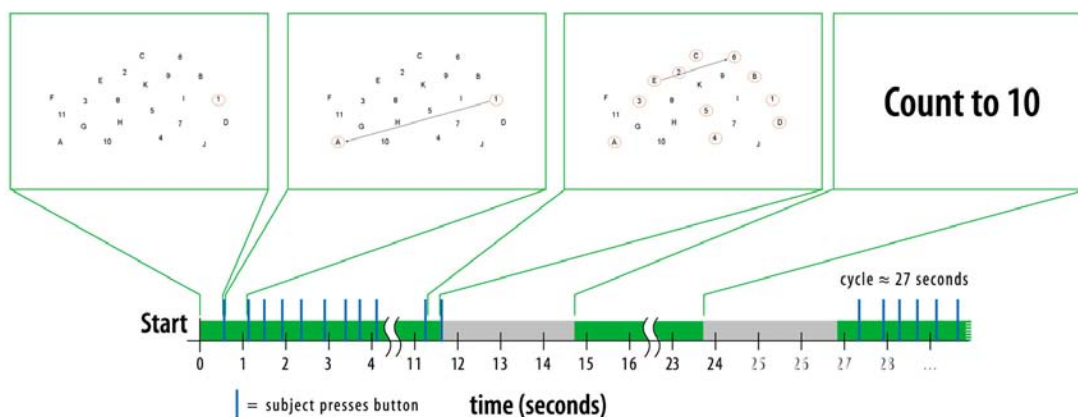
Face Recognition Test

Consistent with the Faces Subtest in the Wechsler Memory Scale, 3rd edition, I used faces as the stimulus. Subjects were shown groups of 15 faces while in the fMRI scanner, and were asked to remember each face. At the end of the scanning session, the subject was shown another group of faces, both novel and previously viewed, and was asked to indicate which faces were ones that were seen previously while in the scanner. Accuracy for this post-test was recorded for each participant. See Table 4 for further description and timing of protocol.

Table 4. Timing of Face Encoding Test

Face Encoding Test
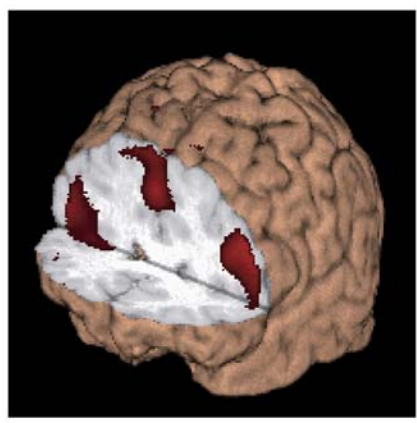
- Requires the subject to view a set of faces, under the instructions that they will have to remember the faces at a later time.
- After a 20-minute delay, the subject must discriminate previously seen faces from novel faces
- Data presented here represent the "encoding" phase of this test only

Memorize Faces

Count to 10

cycle = 30 seconds

Start

0 1 2 3 4 17 18 19 20 21 22 23 28 29 30 …

time (seconds)
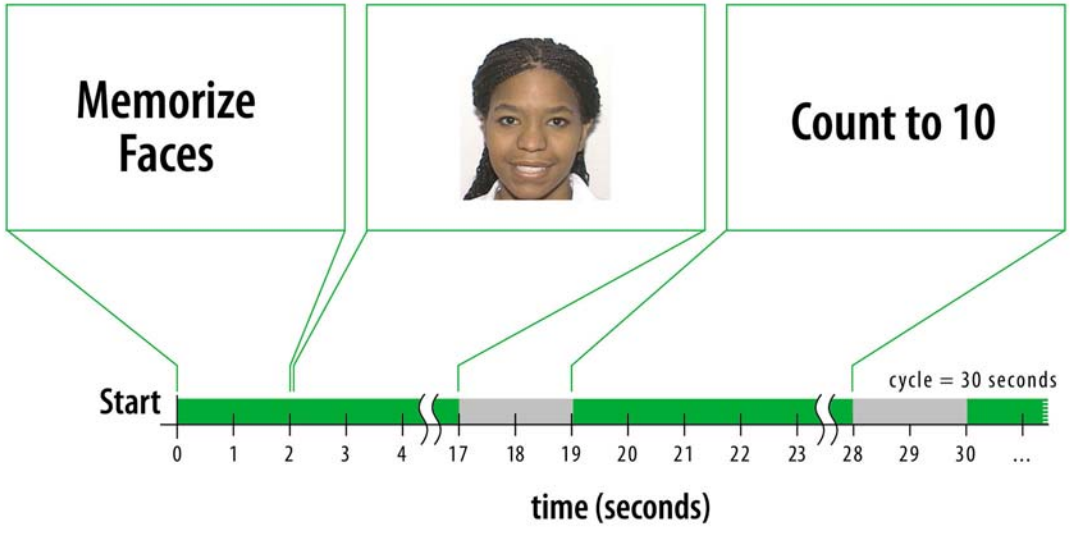
Picture Naming Test

Subjects in the fMRI scanner were be presented with a series of line drawings (Snodgrass, J.G. & Vanderwart, 1980) and asked to silently name each picture, as vocalization while in the scanner produces motion artifacts which may distort the imaging. See Table 5 for further description and timing of protocol.

Table 5. Timing of Picture Naming.

Picture Naming
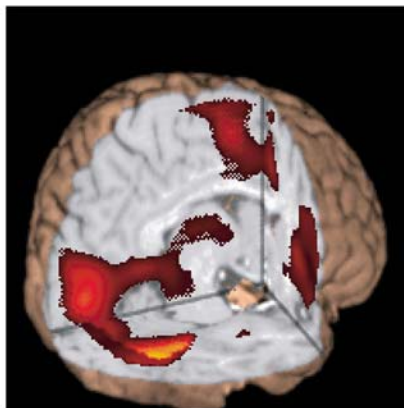
- Modeled after (e.g.) Boston Naming Test
- Subjects produce names of line drawings
- fMRI adaptation requires covert naming responses
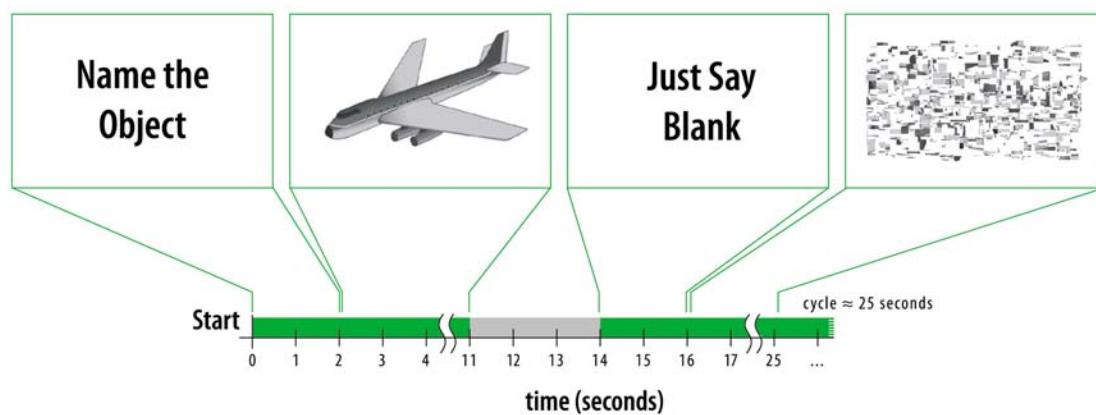
Verbal Fluency Test

While in the scanner, the subject was prompted with a screen that contained the specific instructions: "Please think of as many words that begin with the letter…" A letter then appeared and the subject was instructed to silently think of as many words as he could that began with that letter. The following eight letters were used: F, A, S, C, L, P, R, and W. See Table 6 for further description and timing of protocol.

Table 6. Timing of Verbal Fluency Test.

Verbal Fluency Test
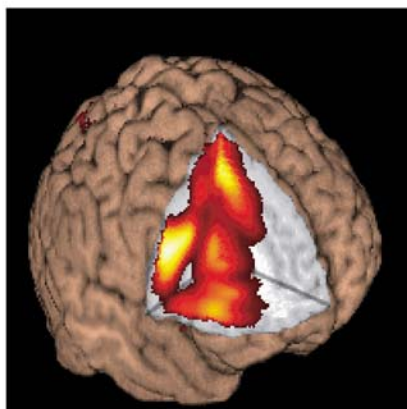
- Common versions of this test use either letters of the alphabet or semantic categories (e.g., animals or fruits) as word generation prompts
- Typical letters used are F, A, S, C, L, P, R, and W
- The VFT is commonly used to assess abstract reasoning and problem solving, as it is as sumed to be sensitive to sequencing, attention, and perseveration.
- For the fMRI adaptation, a time limit of 22 seconds is used

Think of words that begin with ... | C | + | Count to 10

cycle = 31 seconds

Start

time (seconds)
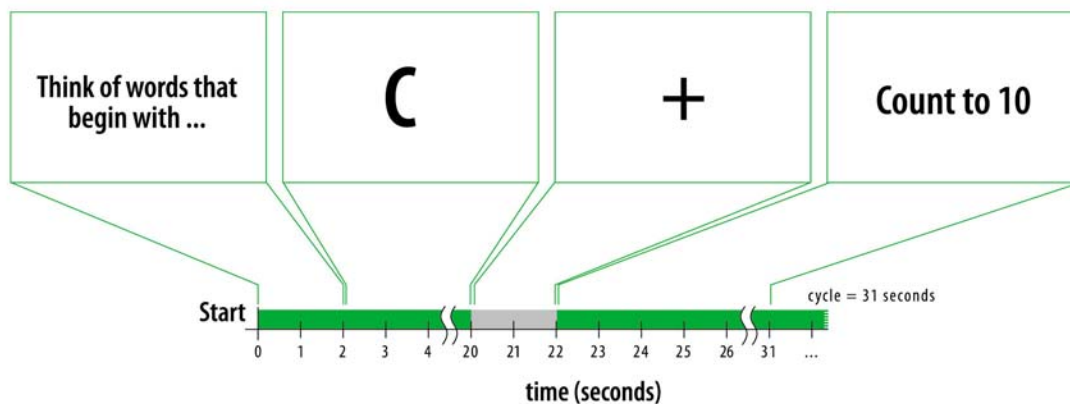
Verbal Working Memory

Subjects in the scanner were offered a list of words, presented one by one. At the end of the list, the subject was prompted to recall silently as many words as he could. This process was repeated 5 times. See Table 7 for further description and timing of protocol.

Table 7. Timing of Verbal Working Memory

Verbal Working Memory
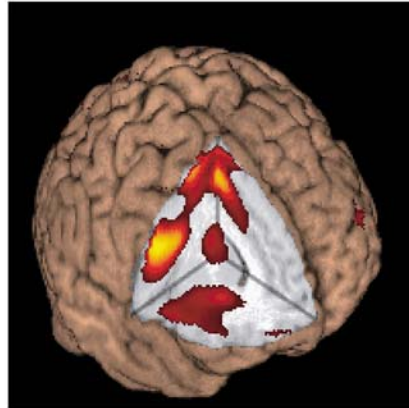
- Modeled after (e.g.) California Verbal Learning Test
- Encoding phase consists of a series of 10 words, presented visually at 1 per second
- Encoding phase is immediately followed by a "repeat" phase (covert rehearsal)
- Analysis epoch includes both encoding and rehearsal phases, as covert rehearsal is assumed to occur during both phases
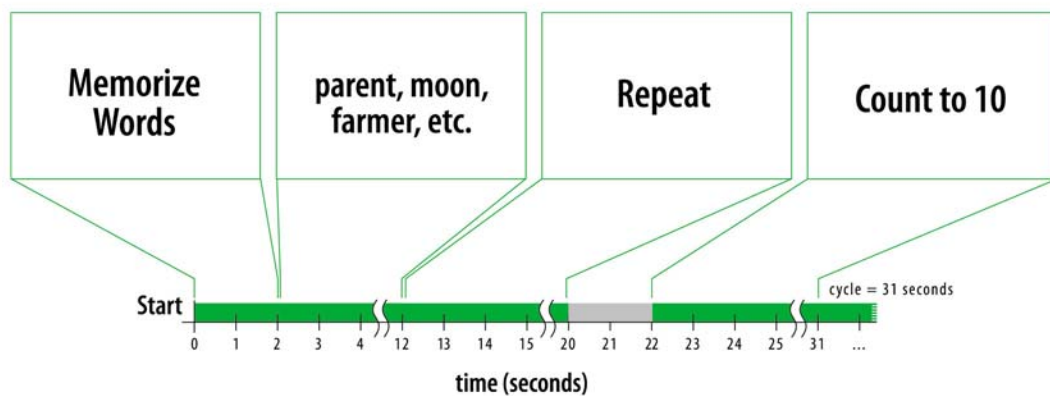
Procedure

MRI scanning was carried out at the Riverwoods Imaging Center (RIC), Provo, UT. This facility is about a 10 minute drive from the BYU campus. Upon recruitment, participants were directed to a web site (braincoglab.net) which included information about the project, the RIC, and maps and driving instructions. This information was provided in written form for those without access to the internet. At this time, the recruiter also determined whether it was safe/appropriate for the potential participant to enter an MRI scanner. For example, those who were pregnant or who had metal implants would not have been allowed to participate (for a complete list of exclusion criteria, please refer to Appendix 1). Upon arrival at the center, participants were met by a member of the research project and invited to review the consent form (Appendix 2) and decide whether to continue. An MRI technician also met with the participant at to make sure that it was appropriate for the participant to enter the scanner.

Functional MRI scanning was carried out by a certified MRI technician along with an fMRI consultant from the Brain and Cognition Laboratory (BYU), under the supervision of an attending RIC radiologist (Figure 2). Each volunteer participated in a session that lasted about 60 minutes, with 25-30 minutes in the MRI scanner. A procedural manual of the scanning process is listed in Appendix3, while a complete manual describing the entire data processing procedure can be found in Appendix 5. A list of the fMRI data processing sequence is also included (Appendix 4).

Figure 15. RiverWoods Scanning Facility

In each scanning session, whole brain images were continuously collected every 2

seconds. A functional scanning protocol was used that was sensitive to blood

oxygenation level dependent (BOLD) effects. In order to do this, I used a gradient echo,

echoplanar imaging sequence. The specific timing parameters used were TE=30ms

TR=2000. 23 Axial slices with 5mm thickness and no gap.

 Data Analysis

fMRI data was processed and analyzed using a sequence of commercial fMRI

analysis software packages. fMRI activation was assessed along two dimensions for each

cognitive test: location(s) of activity foci in the brain, and the intensity of the activation

change(s) for each locus. Group average activation probability maps were constructed

using Matlab software.

FMRI Data was analyzed with statistical parametric mapping (SPM99: Wellcome

Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk.)

according to the following procedure: Prior to statistical analysis, the first four volumes

of each run were discarded in order to avoid T-1 relaxation effects, and the remaining functional volumes from each subject were realigned and resliced with sinc interpolation, using the first volume in the sequence as a reference. Realigned images were motion-corrected and unwarped according to residual motion-related signal changes that were calculated for three rigid translation and three rotation directions. The six motion-correction parameter vectors were then saved for use as confounding covariates in the statistical analysis. A mean image for each subject was created using the realigned and motion-corrected volumes. A T-1 weighted SPGR anatomical MRI was coregistered to this mean image, ensuring that the functional and structural images were spatially aligned. The structural image for each subject was superimposed with the functional activation "hot spots" for display inspection purposes. The images were then spatially normalized to a template provided by the Montreal Neurological Institute (MNI), which is a composite of 305 brain samples. This step was necessary in order to place each participant's brain within a common stereotactic space. Finally, the functional images were spatially smoothed with an 8mm full width at half maximum (FWHM) isotropic Gaussian kernel. Smoothing is necessary in order to create average images across many subjects and as a necessary condition for the application of Gaussian random field theory in group-level statistical inference (Friston, Holmes, Worsley, Poline, Frith, & Frackowiak, 1995). A boxcar waveform convolved with a synthetic hemodynamic response function (HRF) with a 4 second lag-to-peak is used as a reference waveform for each condition. The data are high-passed-filtered using a set of discrete cosine basis functions with a cut-off period of 128 seconds. To condition temporal autocorrelations in the data, an AR1 correction was applied to each subject's data during statistical analysis.

The resulting foci of activation are characterized in terms of peak height and spatial extent. The significance level ($p < 0.5$) of each region was estimated and corrected for multiple contrasts using distributional approximations from the theory of Gaussian fields, both in terms of the probability that a region of the observed number of voxels could have occurred by chance, and the peak height observed could have occurred by chance, over the entire volume analyzed. Regions of significant activation were displayed as "hot spots" in terms of the resulting t statistic for each voxel that exceeded the significance threshold. After statistics were computed for each subject, a group-level random effects model (RFX) was applied. The major benefit of using an RFX model is that only areas with activation consistent in all 26 subjects were able to survive the statistical analysis (Penny, 2003). A complete manual of statistical processing sequence and procedures is found in Appendices D and E, respectively.

Results

Because of the number of subjects, the anatomical image and superimposed functional activation map for each subject was displayed and compared individually, before averaging the scans together, in order to detect any gross deviations or outliers (i.e. a subject without any activation/corrupted data). This strategy avoids sources of error that typically arise when anatomical and functional images are averaged across subjects. Across-subject averaging is often necessary in order to improve the signal-to-noise ratio of functional scans from lower quality MRI magnets.

As stated in the hypothesis, I anticipated patterns of activation to be consistent with previous fMRI findings for similar tasks. Specific areas of activation will be reported for each task individually.

Matrix Reasoning

The mean activation for all 26 subjects included the bilateral fusiform gyri , with stronger activation on the right, bilateral inferior lateral occipital, and inferior middle lateral occipital, both stronger on the right, bilateral thalamus (including inferior and superior thalamus), bilateral frontal operculum (including the basal ganglia, bilaterally), the dorsal processing stream, which extends dorsolaterally from the primary visual areas in the occipital cortex to superior parietal lobule (SPL), including the inferior parietal sulci (IPS).   Although this activation was bilateral, it was stronger on the right than the left. There was also activation in the dorsal anterior cingulate and bilateral medial supplementary motor areas (SMA) , although it was stronger on the left. There is also bilateral precentral gyrus activation, although it was stronger on the left, medial frontal gyrus activation only on the right, and anterior middle frontal gyrus activation only on the left. There was also some evidence of small right fronto-polar activation on the right, and on the tip of the superior frontal gyrus on the left. Please refer to Figure 16.

Figure 16. Matrix Reasoning results.
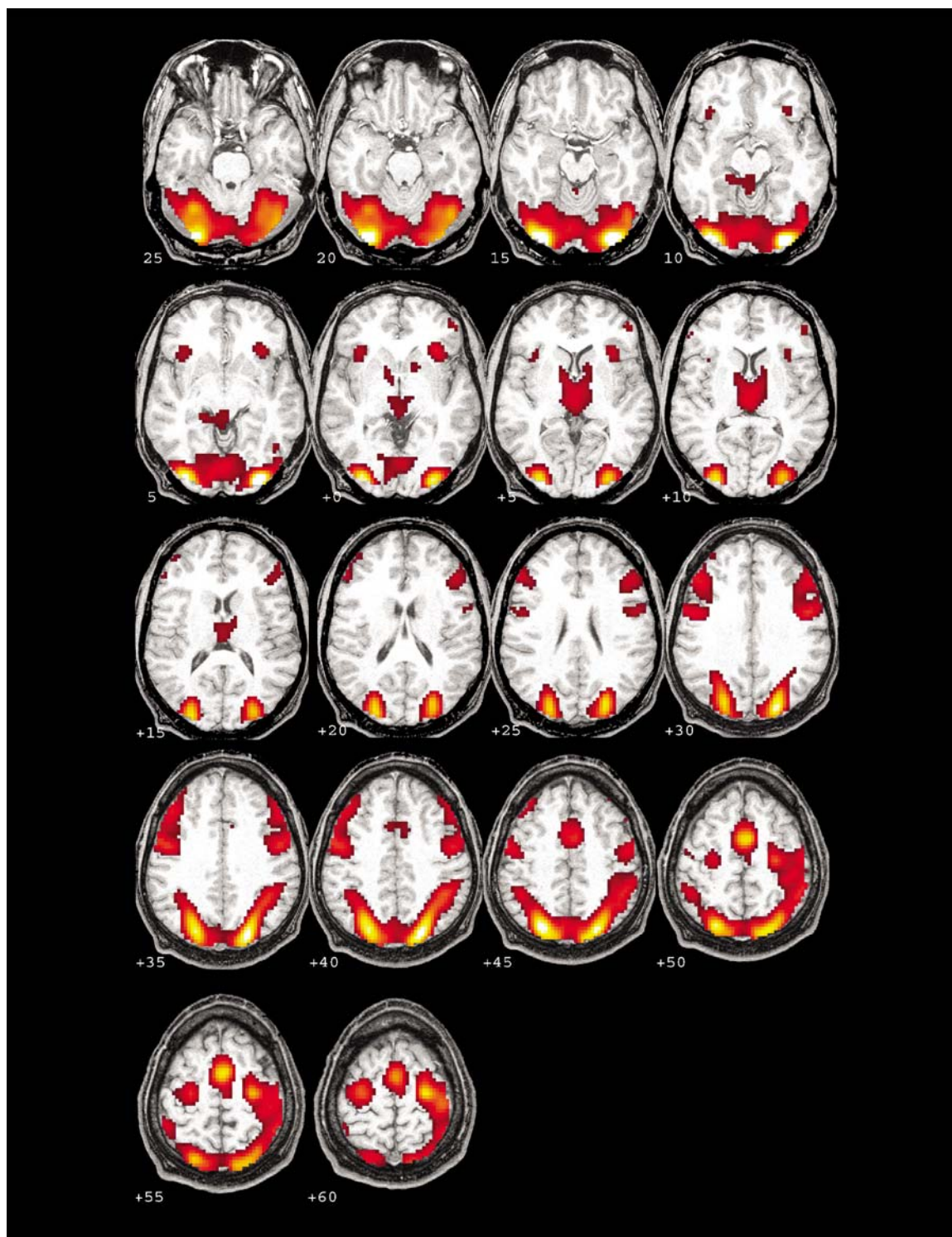
Trail Making Test

The mean activation for all 26 subjects was almost identical to the Matrix task, and included the bilateral fusiform, with stronger activation on the left, small activation in the inferior thalamus, bilaterally, the dorsal processing stream from the LOC to the superior parietal lobule, including the IPS, bilaterally, but with a little stronger extension into the IPS on the left. There was also activation in the left precentral motor cortex, and the left medial SMA. Please refer to Figure 17.

Figure 17. Trail Making Test results.
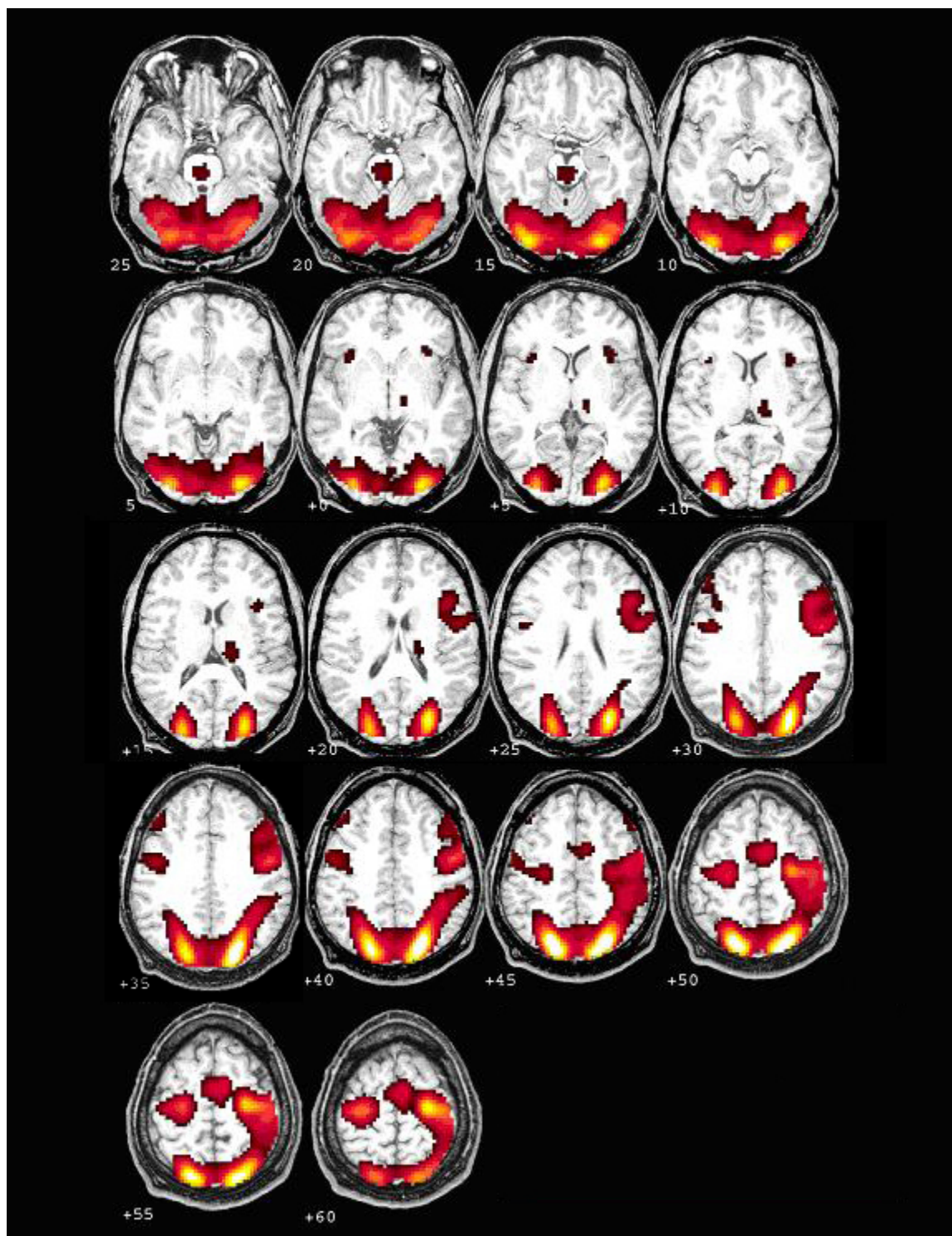
Picture Naming Test

The mean activation for all 26 subjects included bilateral fusiform activation, but much stronger on the right, and some small dorsal processing stream activation, bilaterally. At lower thresholds, mean activation included areas which one would typically expect for a Picture Naming task, including strong left frontal operculum (Broca's area), bilateral anterior cingulate, left speech motor areas, and left thalamus activation. One may have expected to find frontal activation for this task, but due to the use of very common objects, (e.g. chair, airplane, etc.), the simplicity of the pictures would suggest less frontal lobe activation in controls. Pilot studies with dementia patients reveal higher activations in these areas for the same task, which suggests that those who are neurologically impaired require more effort and elicit greater activations for a simple task. For a future study, I predict that if I used more difficult pictures to name, I would see greater activations in these areas for controls. Please refer to Figure 18.

Figure 18. Picture Naming results.
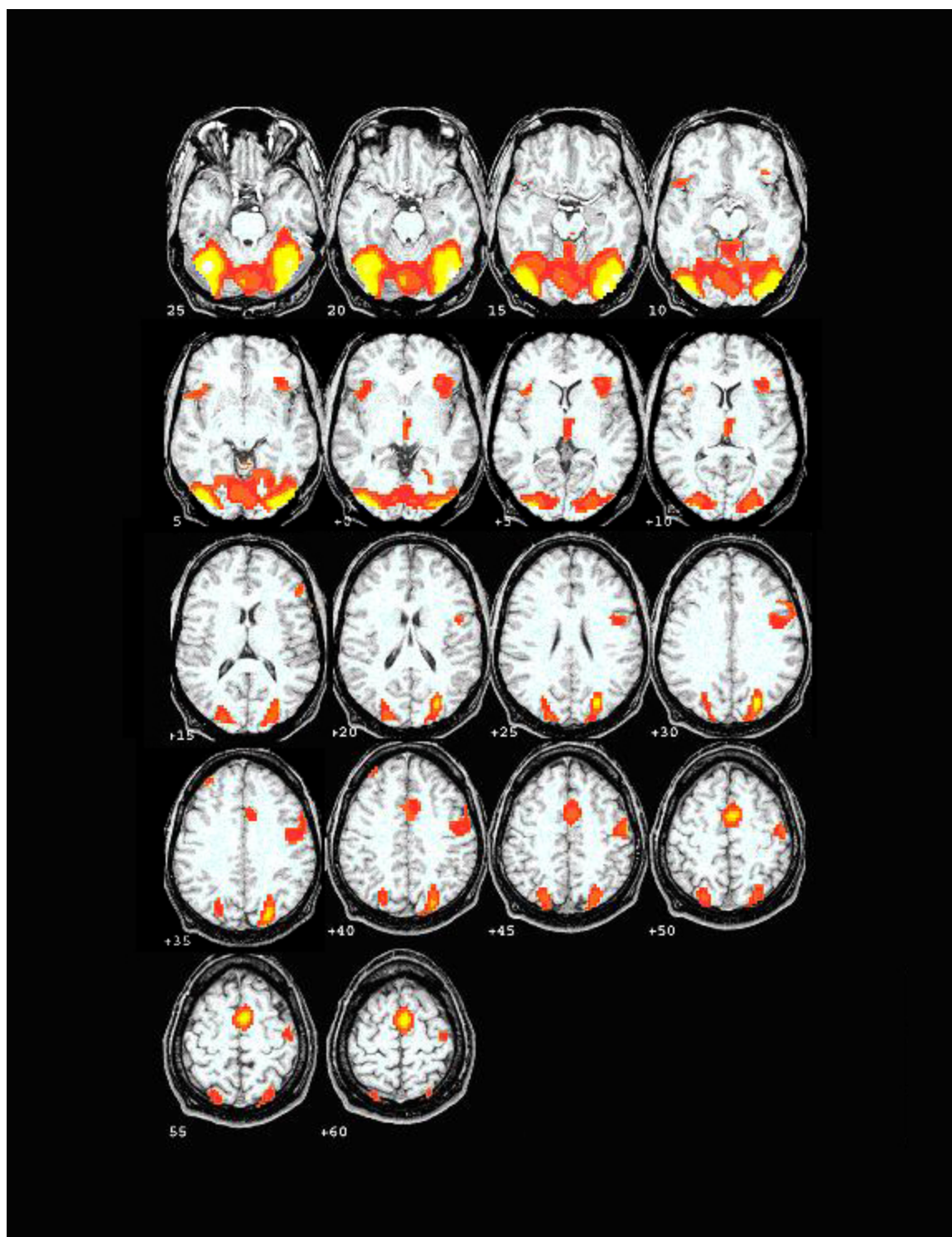
Face Recognition Test

The mean activation for all 26 subjects included the SMA bilaterally, with

stronger activation in the right precentral motor cortex, the left caudate (superior portion),

bilateral fusiform and LOC, but with much stronger activation on the right. There was

also right posterior hippocampal, medial hippocampal, and parahippocampal gyral

activation.   Please refer to Figure 19.

Figure 19. Face Recognition results.
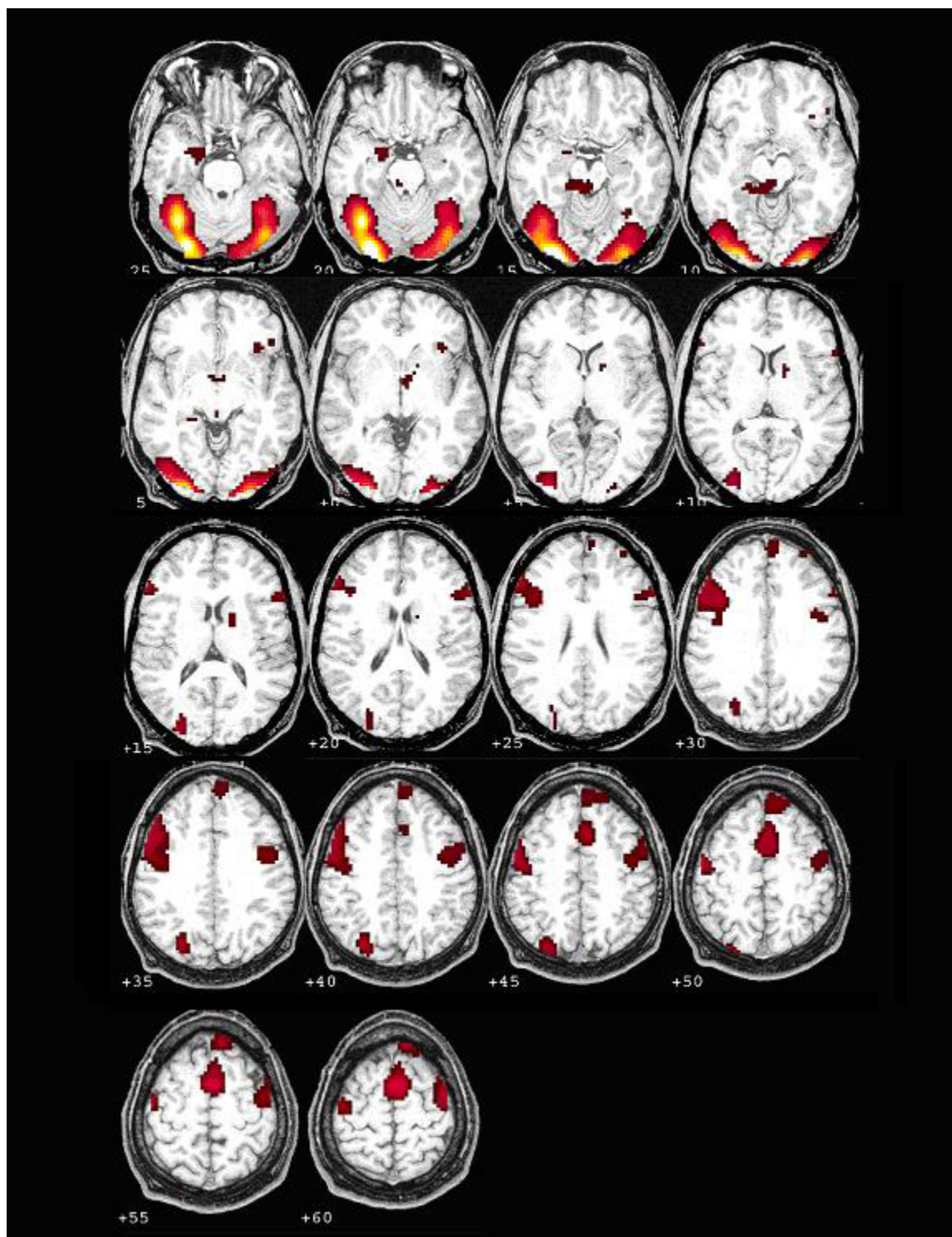
Verbal Memory Test

The mean activation for all 26 subjects included the SMA bilaterally, with a very small activation in the medial frontal gyrus (MFG). There was activation on the left in the speech motor areas, the thalamus, the IPS, the fusiform, and the primary visual cortex (V1). There was also some activation on the right inferior LOC. Please refer to Figure 21.

Figure 20. Verbal Memory Test results.
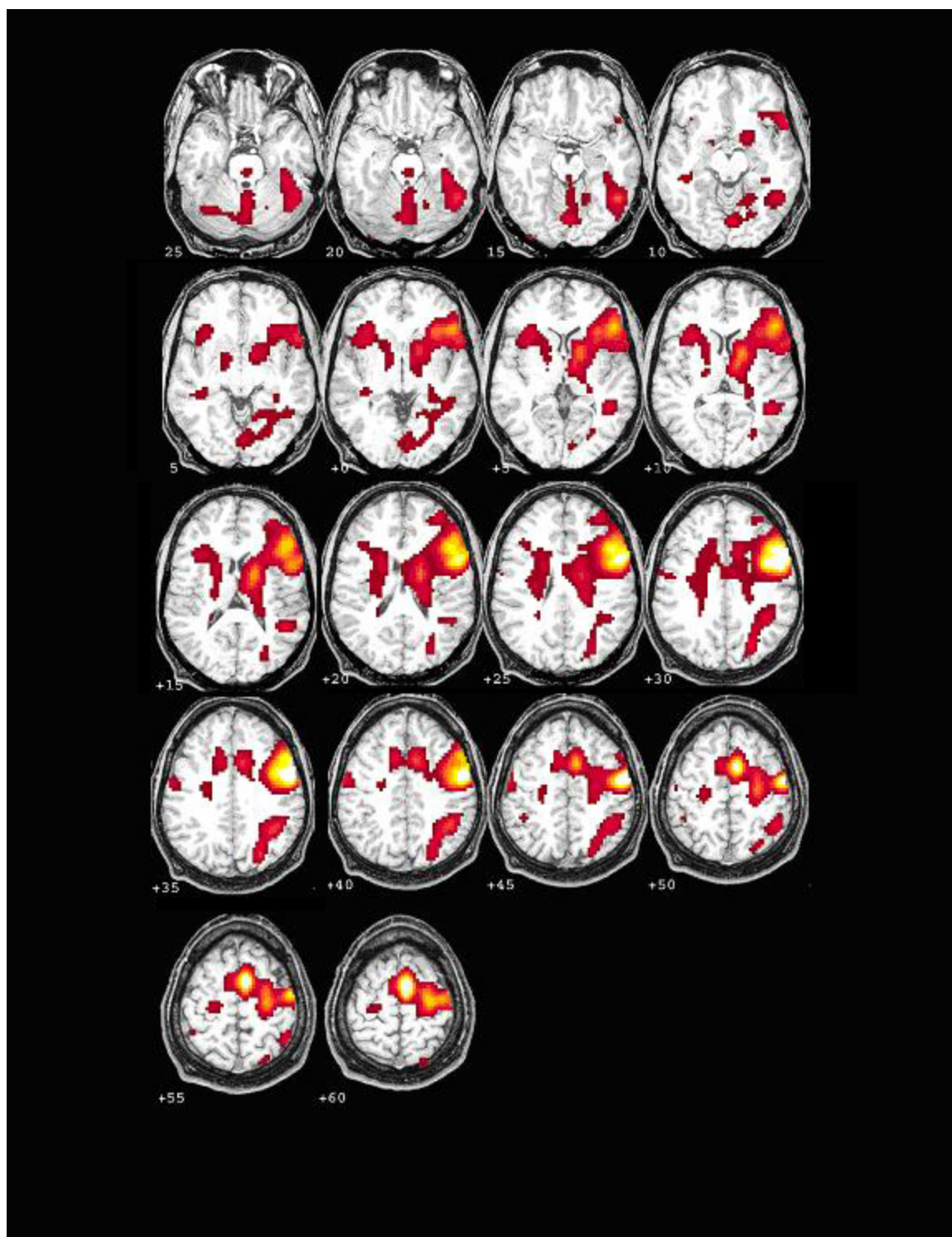
Verbal Fluency Test

The mean activation for all 26 subjects included the left caudate and left frontal operculum, Broca's area (left inferior frontal gyrus which extends to Broca's area), the speech motor cortex, bilateral SMA. Also, out of all the six tasks, this task elicited the greater amount of AC activity. Also, there was no noted activation in visual areas. Please refer to Figure 21.

Figure 21. Verbal Fluency Test results.
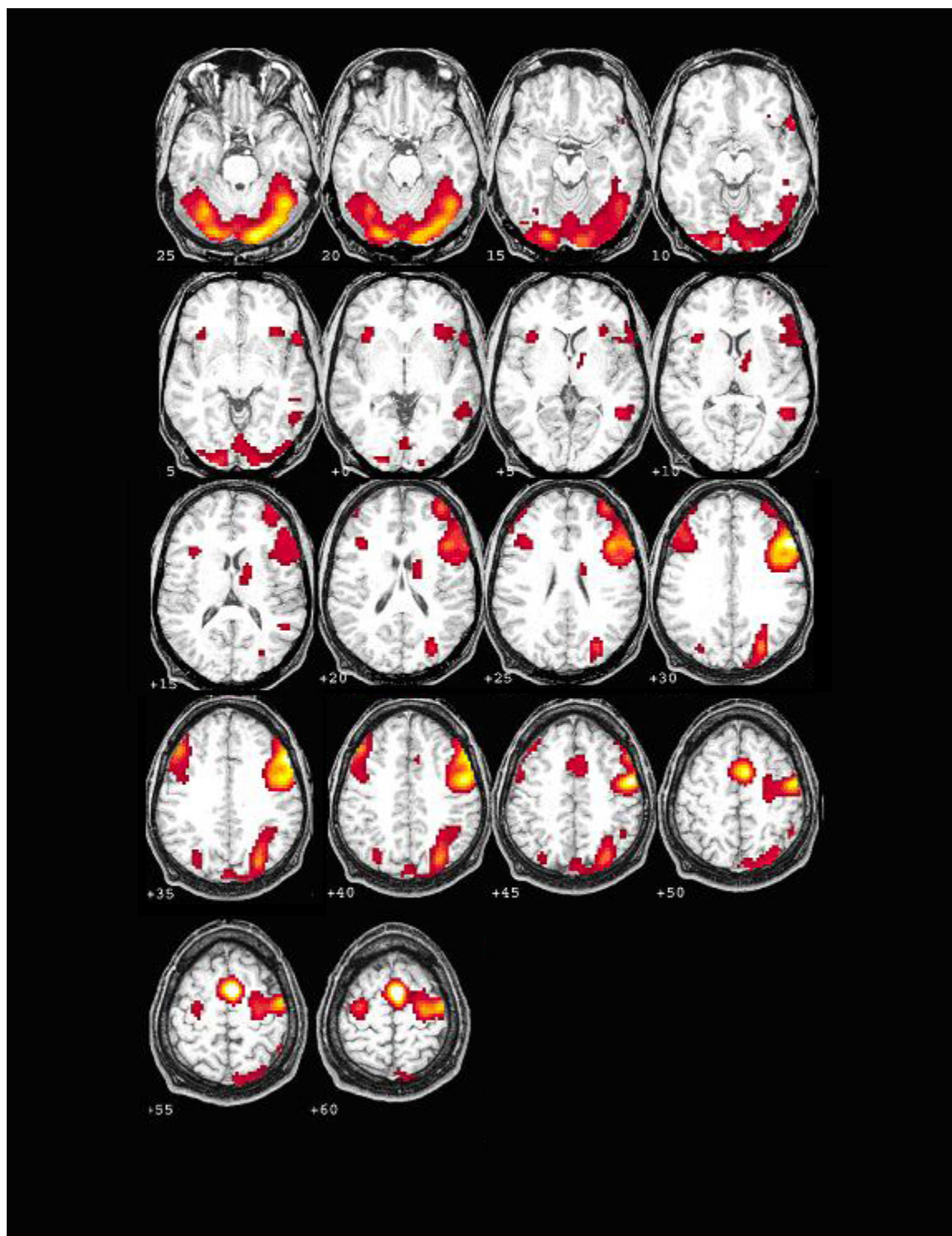
Male versus Female

When comparing 13 male versus 13 female activations for each individual task, I did not find any statistical differences in activation between genders. Although I initially expected to find gender differences on the Picture Naming task, subtracting males from females and females from female yielded no differences. In order to more confidently accept the null hypothesis of no sex differences, we examined the data from all the experiments using the most liberal voxel extent threshold that is scientifically acceptable ($p<0.05$, and cluster extent threshold of 0). These findings suggest that our current technology is not yet at a level that can easily differentiate between genders. As fMRI is still in its nascence, we do not yet have the capability to reliably find gender differences for these particular tasks. It stands to reason that as our tools and technology advance, so will our abilities to more clearly and easily discover gender differences with regard to functional activation. Also, gender differences may be difficult to detect due to the breadth of our analysis. Because I am more interested in general areas of whole brain activation for these tasks, I sacrificed some overall sensitivity for specific regions. For future study, a particular region of interest (ROI), e.g. the anterior cingulate, may be analyzed more closely, increasing the sensitivity to activation for that small area. I would then expect to find more differences due to gender between male and female controls.

Discussion

In general, the fMRI results here are consistent with the traditional assumptions of neuropsychology, in that activation was present for the most part in those brain areas that are assumed and were hypothesized to be engaged by the six neuropsychological tasks I examined in this dissertation. There were, however, a few interesting findings involving

the results of Matrix and the TMTB. One noted deviation, was the observation that the so-called "frontal" tasks (i.e. Matrix and TMTB), engaged large portions of the parietal lobes, bilaterally, in addition to frontal areas. These findings are consistent with growing research that suggests a more prominent role for the parietal lobes in executive functioning than was previously recognized (Collette, 2006).

Yet another interesting finding was the overall, global similarities in activation for both the Matrix and the TMTB tasks. As these tasks are typically administered independently in standard neuropsychological test batteries, they are assumed to measure different cognitive functions: problem-solving and cognitive switching/flexibility, respectively (Lezak, 1995). However, our results suggest that the two tasks elicit and engage analogous areas of the brain, implying that the administration of both tasks in an evaluation may be redundant and ultimately unnecessary.

The absence of consistent gender differences should be noted. As stated previously, gender differentiation in research has scattered findings. To reiterate Voyer's (1996) meta-analysis, the reliability of sex-based lateralization differences in object naming is not entirely clear. There is, however, some reason to believe that men and women might show different brain activation patterns during object/picture, as studies evidence a bilateral verbal processing advantage for women (Shaywitz et al., 1995; Pugh et al., 1996; Jaeger et al., 1998; Kansaku et al., 2000; Phillips et al., 2001; Rossell et al., 2002; Baxter et al., 2003; Gur et al; 2000; Goldstein et al., 2005), while others do not (Frost et al., 1999; Schlösser et al., 1998; Buckner et al., 1995; Price et al., 1996). As stated in the previous results section, we may be limited by our current technology, and future scientific advancements in this field may yield more discriminating results.

Future Directions

 One of the main reasons for this research project was to ultimately provide a useable normative data set that would be useful in clinical settings. My data is available in a format where, if one would request, normative data sets could be derived; however, demonstrating specific clinical cases for each task is beyond the scope of this dissertation, but part of my current work. I can, nevertheless, provide explicit details about how one should use my statistical maps to evaluate outcomes from individual patients against this data set . First, a logical approach would be to divide the brain into functional regions, or regions of interest (Brett et al, 2002). Secondly, one would be able to use any number of summary statistics across subjects which could be plotted in that particular region of interest. For example, one could take the total number of subjects for each region whose activation exceeded a certain threshold peak base. Alternatively, one could compute the distribution of the heights of activation peaks across subjects. For example, if a T-value is set to a certain threshold, one could plot peak values which would equal a distribution that can be transformed into z-scores. Yet another variation and an additional option is to do an analysis of peak activations and the extent of activations within each of the regions of interest, in terms of how many voxels were activated in that particular area. The distribution of the extent of the voxels can then be converted to z-scores with standard deviations, etc.

 I am also interested in variables of interest, including gender, age, socio-economic status, ethnicity, educational level, etc. that may correlate with different patterns of brain activity. As previously stated, I am interested in future studies including in-depth region of interest (ROI) analyses, gender differences with ROI, and increasing the difficulty

level for images in Picture Naming with a prediction that frontal areas will be more engaged. Preliminary studies with dementia patients are already in progress, and I am very interested in studying various impaired populations with this same protocol. Also, this study is limited by age (18-40 years), and I would like to obtain data for all age groups, including children and adolescents.

Although I have offered future directions for my specific dissertation, fMRI research and neuropsychology, as a unified front, has many potential areas of study. For example, mild brain injuries (MTBI) are often overlooked due to structurally intact static MRI images. Although a MTBI may be structurally intact, there are many mild injuries that result in confusion, attention and concentration difficulties, disorientation, and difficulties with problem solving. Therefore, this study could serve as a supplemental tool for diagnosis for the success of classifying abnormal patterns of activation, pre- and post-test. For example, neuro-imaging before treatment would be compared to imaging after treatment, evaluating the success of therapy based on observed brain activations. An early study conducted by (Taber et al, 2003) used fMRI images pre and post treatment for a female with PTSD. Pre-treatment scans revealed heightened brain activity when the patient was merely in a resting state, indicating severe amounts of generalized anxiety. Four weeks after a conventional cognitive behavioral therapy treatment, the patient was scanned again, and it was revealed that her overall activation during a period of rest had decreased dramatically (Figure 22).

Figure 22. Generalized anxiety treated by cognitive-behavioral therapy.
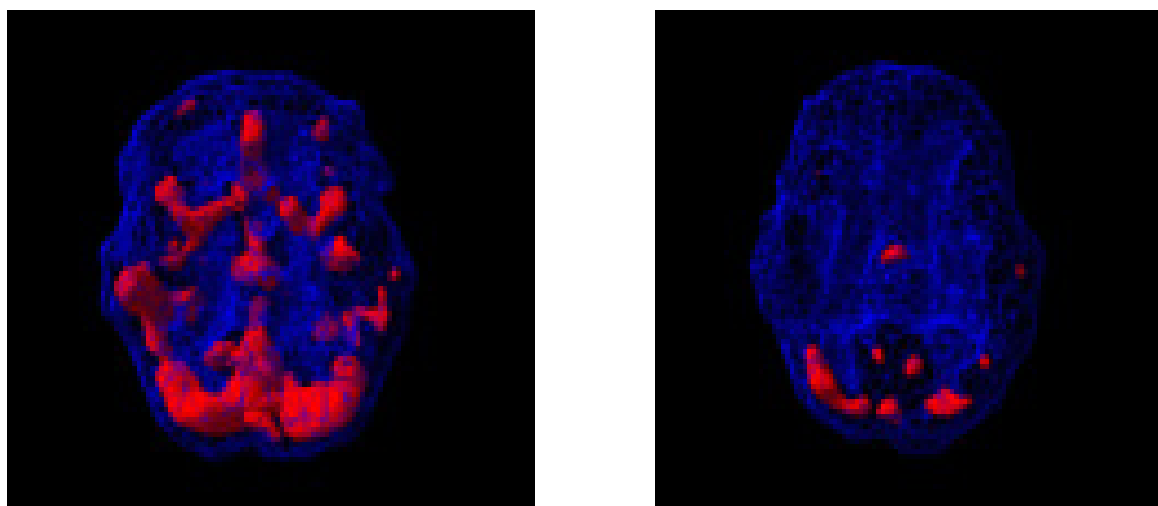
<div align="center">
Pre-treatment   Post-treatment

Baseline fMRI showed increased activity in limbic areas. Four weeks post treatment fMRI shows significant decline in limbic activity.
</div>

Rauch also stated that neuroimaging on a larger scale (PET and CT) could be useful in identifying the neuroanatomy and activation involved in the onset of PTSD. By scanning individuals who are regularly confronted with traumatic situations,(e.g. fire fighters, police, etc.), pre- and post-trauma, one may be able to more clearly isolate the effects of intense traumatic exposure on neurochemistry. Yet another study conducted by Wilde and colleagues (2006) uses imaging to determine the validity and usefulness of a therapy agent, vagus nerve stimulation (VNS), and its effects on depression. They found that nearly 70% of patients who reported a decrease in depression at one year post-treatment, continued to improve at a two-year follow-up. Scanning revealed a significant decrease in activity in the prefrontal cortical regions. Thus, this demonstrates that an important treatment outcome would have gone unnoticed had it not been for neuroimaging data. Finally, a recent study by Cook et al (2006) utilized fMRI as a measurement tool for the effectiveness of Propanalol, an antihypertensive drug, on blood pressure. Again, effects

of treatments, in this case pharmacological treatments, would have gone unnoticed without the benefit of neuroimaging data.

In summary, there are numerous directions for these types of studies. As stated previously, currently, our tools of measurement in this field are relatively crude; e.g. the lack of gender related differences found for each of the tasks is somewhat paradoxical to evidence of gender differences in the effects of stroke, the ensuing cognitive impairments that may occur, and recovery (Snyder, 1991). Although the nascence of fMRI and functional technology lends to less advanced measurement capabilities, I hope that my research contributes empirically to the explanation of natural laws that underpin neuroscience.

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APPENDIX 1 and 2

Riverwoods
IMAGING CENTER

Name _____ Height _____ Weight _____

Birth Date _____ Age _____ Physician's name _____

Briefly describe the physical symptoms you are experiencing or the reason for the exam: _____
_____

How long have you had this problem?
_____

Have you had any previous studies: YES ___ NO ___ (If YES please list)
                  BODY PART   **DATE**   **FACILITY LOCATION**
MRI _____ _____ _____
CT/CAT SCAN _____ _____ _____
X-RAY _____ _____ _____

Are you pregnant or experiencing a late menstrual period?   YES ____ NO ____
Date of last menstrual period _____   Are you breastfeeding   YES ____ NO ____

Have you ever had a reaction to the contrast media or dye used for MRI'S OR CT'S examinations?
YES ____ NO ____ If yes, please describe _____

Do you have a personal history of cancer?   YES ____ NO ____
If yes, what type of cancer was/ is it? _____

Have you been diagnosed, or are you being treated for any medical conditions or illnesses? YES ___ NO ___
If yes, give a brief explanation: _____

YOUR DOCTOR WILL GET A COPY OF THE RESULTS WITHIN A FEW DAYS.

Normally the MRI scan is considered very safe. However, patients with certain implants and foreign bodies may have some problems. *It is important for you to alert the technologist if there is any foreign material in your Body.*

On some examinations I t is necessary to inject a contrast material into your body. It is injected through an IV that may be placed in your arm or hand. Normally, this contrast media is very safe. However, any injection or medication carries with it risks. These risks may include problems from the IV or in the form of a reaction to the contrast. The Physicians and staff of the diagnostic imaging department are trained to treat these reactions. Do you consent to having the contrast Injected if necessary? YES ____ NO ____

We are only able to scan the body part that your Doctor has ordered. Do you consent to having the ordered MRI scan, and to changing into metal free clothing before the exam? YES ____ NO ____

"PLEASE COMPLETE AND SIGN THE OTHER SIDE"

280 West Riverpark Drive, Suite 100 / Provo, Utah 84604 / 801.229.1009

Riverwoods
IMAGING CENTER

Some of the following items may be hazardous to your safety and some can interfere with the MRI examination. Please check the correct answer for the following.
Do you have any of the following?

YES __ NO __ CARDIAC PACEMAKER
YES __ NO __ IMPLANTED CARDIAC DEFIBRILLATOR
YES __ NO __ ANEURYSM CLIP(S)
YES __ NO __ NEUROSTIMULATOR
YES __ NO __ INSULIN OR INFUSION PUMP
YES __ NO __ IMPLANTED DRUG INFUSION DEVICE
YES __ NO __ BONE GROWTH/FUSION STIMULATOR
YES __ NO __ COCHLEAR, OTOLOGIC, OR EAR IMPLANT
YES __ NO __ ANY TYPE OF PROSTHESIS (EYE, PENILE, ETC)
YES __ NO __ HEART VALVE PROSTHESIS
YES __ NO __ ARTIFICIAL LIMB OR JOINT
YES __ NO __ ELECTRODES (ON BODY, HEAD, OR BRAIN)
YES __ NO __ INTRAVASCULAR STENTS, FILTERS, COILS
YES __ NO __ SHUNT (SPINAL OR INTRAVENTRICULAR)
YES __ NO __ VASCULAR ACCESS PORT AND/OR CATHETER
YES __ NO __ SWAN-GANZ CATHETER
YES __ NO __ ANY IMPLANT HELD IN PLACE BY A MAGNET
YES __ NO __ TRANSDERMAL DELIVERY SYSTEM (NITRO)
YES __ NO __ IUD OR DIAPHRAGM
YES __ NO __ TATTOOED MAKEUP (EYELINER, LIPS, ETC.)
YES __ NO __ BODY PIERCING(S)
YES __ NO __ ANY METAL FRAGMENTS
YES __ NO __ INTERNAL PACING WIRES
YES __ NO __ AORTIC CLIP
YES __ NO __ METAL OR WIRE MESH IMPLANTS
YES __ NO __ WIRE SUTURES OR SURGICAL STAPLES
YES __ NO __ HARRINGTON RODS (SPINE)
YES __ NO __ METAL RODS IN BONES
YES __ NO __ JOINT REPLACEMENT_____
YES __ NO __ BONE/JOINT PIN, SCREW,NAIL, WIRE, PLATE
YES __ NO __ HEARING AID (REMOVE BEFORE MRI)
YES __ NO __ DENTURES (REMOVE BEFORE MRI)
YES __ NO __ AN INJURY TO THE EYE INVOLVING A META-
LLIC OBJECT?
OTHER, Please explain:_____

Please mark on the figure below, the location of any implant or metal inside of or on your body:

Right   Left
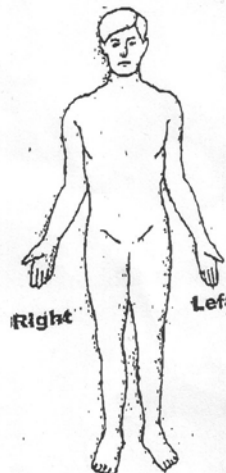
Before your MRI, please remove all metallic objects including keys hair pins, barrettes, jewelry, body piercing, bra, watch, safety pins, paperclips, money clips, credit cards, coins, pens, belt, metal buttons, pocketknife, & clothing with metal in the material.

NOTE: YOU ARE REQUIRED TO WEAR EARPLUGS OR EARPHONES DURING THE EXAM

Signature of Person completing Form _____ Date_____

Form completed by: PATIENT __ RELATIVE: _____
                                               Name & Relationship to patient

                    OTHER: _____
                                               Name & Relationship to patient

280 West Riverpark Drive, Suite 100 / Provo, Utah 84604 / 801.229.1009

Riverwoods
IMAGING CENTER

PATIENT HISTORY SHEET

(Please print)
PATIENT'S NAME _____ DATE_____

REFERRING PHYSICIAN _____

1.- Have you had an MRI or CT on the part of your body in which the procedure is to be performed?   YES _____ NO _____
2.- At which facility was your MRI or CT performed?_____
3.- What is the level of intensity of your pain at this time on a scale of 0 to 10, with 0 being no pain and 10 being the greatest pain? _____

4.- Have you had surgery on the part of your body being scanned today? YES _____ NO _____
5.- If you did have surgery, how long ago was this surgery performed? _____

6.- Describe the location of your pain _____

7.- Shade in the area of pain, numbness, and/or tingling:
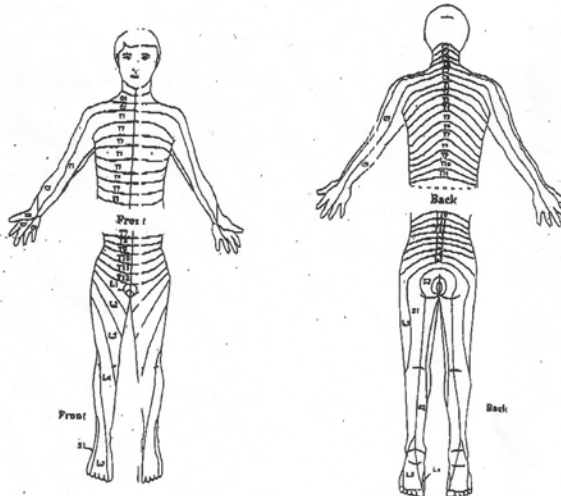
(For pain management procedures), What is the level of pain at discharge? _____

280 West Riverpark Drive, Suite 100 / Provo, Utah 84604 / 801.229.1009

APPENDIX 3

BYU FUNCTIONAL NEUROIMAGING LABORATORY
FMRI SCANNING PROTOCOL
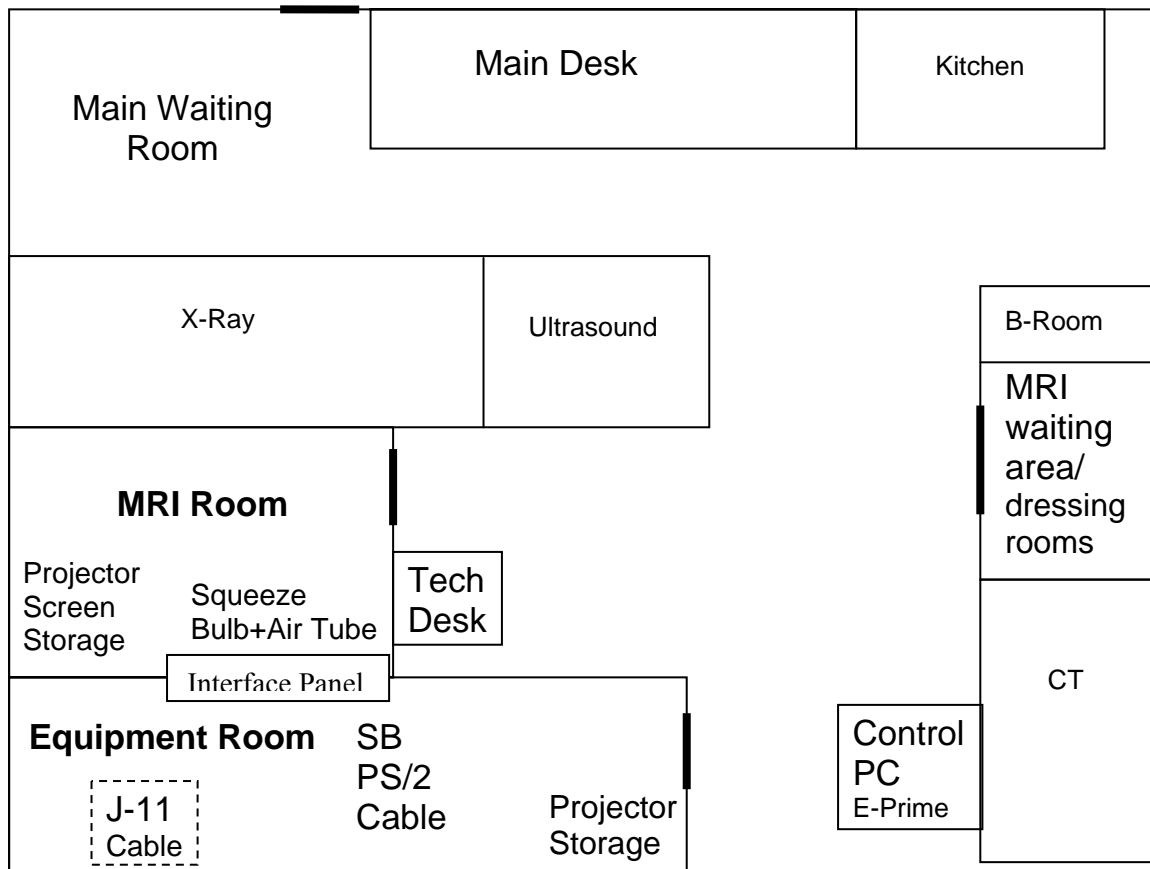### MARK D. ALLEN, PH.D.

OVERVIEW

There are 6 fMRI exams:

	Run Time	Phases	LogFile	Patient Response
MATRIX	4min	124	Yes	Yes
TRAILS	4min	124	Yes	Yes
PNAMING	4min	124	No	No
FET (face encoding test)	4min	124	No	No
VMT (verbal memory test)	4min	124	No	No
VFT (verbal fluency test)	4min	124	No	No

*We prefer to use the term *exam* (rather than *experiment* or *test*), because it sounds best to patients.

*Never refer to an exam as an *experiment* to a patient.

After the functional runs, the subject/patient will also undergo 1-3 structural scans.

SCHEMATIC PLAN OF THE RAIC

	Main Desk	Kitchen
Main Waiting Room		

X-Ray	Ultrasound

B-Room

MRI waiting area/ dressing rooms

MRI Room

Projector Screen Storage Squeeze Bulb+Air Tube Tech Desk

Interface Panel

CT

Equipment Room SB PS/2 Cable

J-11 Cable

Projector Storage

Control PC E-Prime

SETUP

There should be at least two FNL associates at each scan. One person should arrive at least 15min. before the patient is scheduled to arrive. Normally the patient is asked to come at least 20minutes before s/he is scheduled to go into the scanner. If it is a patient scan, be sure to *dress nicely* and try to give the impression that you are a competent professional. This is very important.

Often times there will be an MRI scan in progress when you arrive. The following 5 steps can be done during this time without interrupting any sessions already in progress.

1. The first person to show up should ask someone at the front desk for the requisition form ("req. form") for the patient/subject.
2. Unroll the grey PS/2 cable that comes from the SB (squeeze bulb) interface mouse and carefully string it out into the control room toward the Control PC.

a. The SB cable is actually a series of 3 cables, so make sure all the connections are tight after you roll it out.
3. Unroll the grey PS/2 cable on the right of the Control PC.
   a. This cable is plugged into the PC at one end with an open connector at the other end.
4. Plug together the loose ends of the SB cable the PC cable.
5. Restart the Control PC computer.
   a. *Be sure to check if there are any important programs running first*
   b. After restart, the computer will instruct you to press ctrl-alt-delete to login into windows.
   c. A login name will appear on the login menu. The password is the same as the login name.
6. Bring the projector, the projector platform, and the platform adjuster out of the equipment room.
   a. Unroll the projector cable and setup the projector platform unit on the sill of the control room window.
      i. The projector cable is stored under the Control PC desk.
   b. Plug the projector cable into the "computer" port on the projector.
   c. Plug the projector power into any available power outlet.
      i. If no outlet is available, ask a tech what you can unplug.
   d. Place the projector so the lens is about 5" from the window surface.

THE PATIENT
   Note: Special procedures for experimental control subjects are covered below
The patient may arrive while you are setting up. They will first fill out insurance forms etc. in the waiting room. When the tech is ready, s/he will go get the patient and bring them back to the dressing room. Let the tech handle this part. However, sometimes the tech gets distracted and forgets to tell you when the patient is dressed and ready.

If the patient is still filling out forms in the MRI waiting room, let them finish, unless you are really pressed for time, in which case tell them that they can finish the forms after the scan.

Instructions, Training, and Patient Preparation.
- Greet the patient by name (get it from the req. form) and introduce yourself.
- Ask them if they have had an MRI before, and tell them that this will be a special kind of MRI scan in which we will be looking at activity in their brains as they perform different mental tasks (e.g., such as memorization and problem solving). Reassure them that the tasks are fairly easy and that we aren't looking for perfect performance, but that it is very important that they try to do the best they can. It's a good idea to mention that the harder they try, the better the results they will get.
- Explain to the patient that they will be lying down on the scanner bed, but that they will be able to see in front of them through some mirrors, and that we will be showing them words and objects on a projection screen in front of them.
  o Try to do this with the scanner room in view, so they can look at the scanner while you are talking to them.

- Tell the patient that they will be able to practice the tasks. Lead them to the Control PC computer, and sit them in front of it.

For instruction on running the practice sessions, see section below: Running E-Prime Experiments.

- Next, the patient will practice the first three exams only (MATRIX, TRAILS and PNAMING).
- Make sure the patient understands each task.
    - Let them practice a couple of times if they need to.
    - Make a note of any performance difficulties (e.g., on the back of their req. form).
    - Be sure to describe the squeeze bulb and how they will use it to respond.
- ***Be sure to tell the patient that it is extremely important to remain as still as possible during the exams. You should remind them of this frequently.***
- Tell them that after they are done with these three exams, there will be three more "easy" exams, which you will explain later on.
- When the practice session is finished, let the tech know that the patient is ready to go into the scanning room.

If two or more lab associates are present (as should normally be the case),
- One person should remain in the control room and:
    - start-up the first E-prime exam (MATRIX, see instructions below).
    - turn on the projector.
    - get ready to adjust the projector position if needed.
- Another person should go into the scanning room with the patient and:
    - set up the projection screen (often the tech has already done this).
    - adjust the position of the projection screen, in coordination with the person outside, so that the patient can clearly see the calibration image (see description of *cal image* below).
        - You have to wait until the patient has been fully retracted into the scanner.
    - unravel the SB (squeeze bulb) air-tube and place the SB in the patient's right hand—assuming the patient has a right hand.
        - The SB is kept in a spot near the interface panel in the MRI room.
    - Get ready to walk the patient through the initial SB test for MATRIX.

Additional Important Issues:
- Communicate regularly with the patient through the console intercom (the tech can show you how):
    - Let the patient know when an exam is about to begin.
    - When there are long down-time pauses due to technical glitches and the like, let the patient know you haven't forgotten about them.
    - Periodically remind them to keep holding as still as possible during the scans.
- ****Monitor the projector at all times in case it cuts out during a session.

The instructions for VMT, VFT, and FET can be given through the intercom.

- o Because these exams are fairly simple, patients will not need to practice them. However, be very clear in your instructions.

RUNNING E-PRIME®™ EXPERIMENTS
- All E-Prime experiments are in a folder called **fMRI_scripts** on the desktop of the Control PC.
  - o Each exam is in its own folder within **fMRI_scripts**
- **To abort an e-prime program while it is running, press <u>ctrl-alt-shift</u>.** But be careful about when you abort (e.g., don't abort during the "left over time" in MATRIX or TRAILS; see below).

Practice Sessions
1. MATRIX
   - Practice.
     - o In fMRI_scripts\MATRIX Click on the program file **PracticeMatrix.es**
     - o E-Prime will launch and open this exam.
       - Click on the **Run** icon (a little purple running man) on the toolbar at the top.
       - Click yes to each of the ensuing dialog buttons.
       - The first test item will appear. Explain the task to the patient.
       - Advance through the first practice item using the mouse, then let the patient advance through the rest to give them sort of a feel for what they will be doing with the SB in the scanner.
       - The practice exam will end automatically.
       - Close the program and go to fMRI_scripts\TRAILS.

2. TRAILS
   - Practice.
     - o In fMRI_scripts\TRAILS Click on the program file **PracticeTrails.es**
       - Advance through a couple of the practice items yourself using the mouse, then let the patient advance through the rest of the items.
       - The practice exam will end automatically.
       - Close the program and go to fMRI_scripts\PNAMING.

3. PNAMING
   - Practice.
     - o In fMRI_scripts\PNAMING click on the program file **PracticePnaming.es**
       - Advance through the practice items using the spacebar. Do all the spacebar presses yourself to simulate the automatic presentation that the patient will experience in this exam.
       - There will be one block of 4 test items, and one block of 4 control items.

- Close the program and go to back to fMRI_scripts\MATRIX in preparation for the start of the scanning session.

Test Sessions
- Before each functional run, the tech will probably ask you for the name of the exam.
  - o Use the names on this document.
- The tech will also ask you for the number of *phases* you need for each exam. It is **124** for all exams.
- The first 2 exams (MATRIX and TRAILS) require log files. This is because the timing of events is not fixed and must be recovered from patient response times recorded in the log files.
  - o Log files are automatically generated at the startup of these two experiments when you are prompted to enter subject ID numbers.

MATRIX.
- In fMRI_scripts\MATRIX Click on the program file **Matrix.es**
- When you run the program, a dialogue box will prompt you for a *subject number*.
  - o Enter the current date in four-digit format: *mm/dd*.
  - o A log file will now be collected during the run with this number as its name.
- A matrix array will appear first for visual ***calibration***.
    - ▪ Calibration means making sure the patient can see the whole display.
  - o The patient will have already seen this array from the practice session.
  - o With the projector now turned on, use this first item for calibration.
  - o Calibration may take a coordinated effort between the projector, the screen, and the mirrors in the head coil.
- Test the squeeze bulb.
  - o The person in the scanner room will have the patient squeeze the SB once.
    - ▪ If the image advances to the next item, you will know the SB is working.
  - o Have the patient squeeze the SB twice more. Two more items will appear and disappear with each squeeze (the patient will have already seen these items from the practice session). This will give the patient a feel for the sensitivity of the SB.
  - o After the 3 practice items, a "WAIT" screen will appear, and the program will not advance any further, until you press the space-bar on the Control PC (But don't do that yet!)
- At this time the patient is ready for the functional scan.
  - o Please see *advanced details for functional scans* below.
- The tech will first do a sagittal localizer scan.
  - o Once the sagittal image is displayed, the tech may ask you where you want the slices placed for the EPIs (functional slices). If you don't know, just say "be sure to get the very top of the brain."
- Other parameters that the tech will probably remember (but might forget) are:

- o 5mm slices
- o TE = 40ms
- o TR = 2000ms
- o Flip Angle = 90
- At this point, with the patient still waiting, the tech will collect one set of EPIs (takes 2 seconds) in order to look at the quality of the functional scans.
- Next the tech will do a short pre-scan (shimming) that takes a couple of seconds.
  - o When s/he tells you the scan is all ready, do the following:
    - Tell the patient the exam is about to begin (through the intercom).
    - Go to the PC and tell the tech you are ready.
    - The tech will start the scans, which you will hear.
    - **The very instant you hear the scans start, press the space bar.**
- The Matrix scan will last 4 minutes and 8 seconds.
- The patient might finish the items before the scanning stops.
  - o If this happens, just let the full 4min.8sec. run out.
  - o Some patients might finish as much as 1 minute early.
- The patient might not be finished with the exam when the scan stops.
  - o If this happens, let the patient finish the exam, letting the E-prime program end on its own.
    - **DON'T** abort the e-prime script, or else no log file will be collected.
  - o If the scanning has stopped and the patient is taking a REALLY long time, turn off the projector and then advance through the remaining items yourself with the PC mouse.
- After MATRIX finishes on its own (i.e., the patient finishes), close the program and go to fMRI_scripts\TRAILS.

TRAILS
- In fMRI_scripts\TRAILS, run the program **Trails.es**
- Enter the current data in four-digit format: mm/dd.
- A calibration screen will appear with an oval-like pattern of numbers and letters.
  - o You may need to adjust the projector/screen.
- Remind the patient what the exam is about.
- The tech will not normally need to do another sagittal localizer.
- The tech might ask you how many phases you want
  - o If not, make sure they prescribe the right number (**124**)
- When the tech says everything is ready synchronize the start of the program with the start of the scanning.
- As with MATRIX, if the exam is still running when the scanner stops (the patient is still working on it), just let the program finish and close on its own.
  - o Unlike MATRIX, subjects won't ever go very far past the end of the scan.

PNAMING
- Run the script **Pnaming.es**

- No ID log is required for this exam, or any of the remaining exams.
- A box will appear for the calibration screen.
    - This is where the pictures will appear.
- Synchronize the start with the tech.
- The program has a fixed length and will therefore end at the same time as the scanning (or within a few milliseconds).

FET, VMT, and VFT
- Procedures are the same as for PNAMING above.

CLEAN UP
Most clean-up can be done while the patient/subject is getting the structural scans.
1. Unplug the projector cable, coil it up and put it back under the Control PC desk
    a. You might let the projector cool off some more while you do this.
2. Unplug the SB cable, roll it up, and put it back in the Equipment Room.
3. When the projector has cooled off, put it away.

TRANSFERRING LOG FILES TO BRAINCOGLAB.NET
The log files from MATRIX and TRAILS need to be transferred to ftp://braincoglab.net.
- The log file from the MATRIX session will be in the **fMRI_scripts\MATRIX** folder.
    a. It will be labeled Matrix-**mmdd**-1.edat
        i. mmdd is the patient ID number that you entered at the startup.
- The log file from the TRAILS session will be in the **fMRI_scripts\TRAILS** folder.
    a. It will be labeled Trails-**mmdd**-1.edat
- Open explorer and select **braincoglab.net** from the favorites.
    a. If it's not in favorites, type ftp://braincoglab.net in the navigator bar.
    b. The login is 'teo'
    c. If you don't know the password yet, be sure to ask Dr. Allen.
- Open the **fMRI_LogFiles** folder.
    a. Put the Matrix log in the Matrix subfolder and the Trails log in the Trails subfolder.
        i. You can just click and drag.
    b. The connection at the Riverwoods is super fast. Transfer should take less than a second.

EXPERIMENTAL (CONTROL) SUBJECTS
- Control subjects should be run after 6:30pm. The center is rarely very busy after about 6:00pm.
- The procedures are generally the same as those for patients.
- Because of the way we recruit subjects, the control subject will usually already know one or more FNL associates.
    a. One of these associates should try to be at the scan and meeting the subject in the main waiting room.

- Directions for getting to the Riverwoods Advanced Imaging Center can be found at http://braincoglab.net/fmri
- A lab associate should meet the subject in the front waiting room and take them directly back to the MRI waiting room.
    a. If you don't intercept the subject, sometimes the receptionist will have them start filling out insurance forms, which they don't need to do.
        i. However, control subjects will fill out a standard screening form and a short medical history form.

If you are recruiting a subject, give them these additional instructions:
1. If the subject wears glasses and also has contacts, contacts should be worn.
2. The subject should avoid fatty foods 12 hours prior to the scan.
3. If the subject drinks caffeine, tell them to come to the scan with their caffeine level a little bit higher than what it normally is at that time of day.
    a. Caffeine has vasoconstrictive effects, which helps BOLD contrast sensitivity.
    b. Caffeine should be ingested fairly close to the time of the scan.
        i. Effects peak about ½ hour after ingestion.

OTHER IMPORTANT ISSUES
1. Be extra sure to take off all metal items on your person before entering the scanner.
    a. Check twice, and then once more.
    b. Magnetic strips (e.g., credit cards) will get erased in the scanner room.
2. Don't ever open the scanner room door while the scanner is running.
    a. If you are inside the room when it starts, you'll have to wait until the end of the scan to leave.
        i. There are earplugs in the top drawer of the large cabinet near the scanner.
3. Don't talk to the techs when they look really busy or frustrated.
4. Have a note-pad handy to write down anything that happens during the sessions that might be relevant to the way the data are processed and/or interpreted.
    a. The backside of the patient req. form is also a convenient place to do this.
5. Be careful not to say anything to a patient that could be construed as *medical advice*.

APPENDIX 4

fMRI Data Processing Sequence

1. Get CD from Riverwoods
2. Put **ref*mmdd*.dat** into **zRefDatTemp** folder (FUSTER)
    a. Copy **ref*mmdd*.dat**--Change name to **ref.dat**
3. Transfer data to ftp://braincoglab.net/fmridata
    a. Create new Subject ReconFolder
        i. Use **zReconTemplate** on FUSTER
        ii. Copy folder to braincoglab
    b. Transfer Pfiles from CD to braincoglab
4. Make subject folder using zProcessingTemplates
5. Transfer copy of subject's **ref.dat** into each folder
6. Notify danchanbyu@gmail.com "files ready to recon"
7. Reconstruction happens
8. Transfer .sdt files to FUSTER
9. Make vectors.doc
10.   Preprocess
11.   L1 Stats
12.   L2 Stats
13.   Normalize SPGR
    a. Coregister
    b. Change voxel size in defaults
    c. Normalize

BYU FUNCTIONAL NEUROIMAGING LABORATORY fMRI DATA PROCESSING MANUAL

OVERVIEW OF DATA PROCESSING SEQUENCE

I. Download raw stimulate.sdt files from ftp://braincoglab.net
II. Convert files to Analyze format using MRIcro software
III. Apply pre-processing sequence using Matlab/SPM software
    a. Slice timing Correction
    b. Realign and Unwarp
    c. Spatial Normalization
    d. Spatial Smoothing
IV. Perform Level 1 statistical analysis using Matlab/SPM software.

SUMMARY OF TIMING PARAMETERS FOR STATISTICAL ANALYSIS

MATRIX
Onset Vector:	[*Subject Specific*]
Duration Vector:	[*Subject Specific*]

TRAILS
Onset Vector:	[*Subject Specific*]
Duration Vector:	[*Subject Specific*]

PNAMING
Onset Vectors:
Fruit:	[1 25 49 73 97]
Tools:	[13 37 61 85 109]
Duration:	4.5

FET
Onset Vector:	[1 16 31 46 61 76 91 106]
Duration:	7.5

VMT
Onset Vector:	[1 16 31 46 61 76 91 106]
Duration:	9

VFT

Onset Vector: [1 16 31 46 61 76 91 106]
Duration: 9

I. DOWNLOAD RAW STIMULATE FILES

- Logon to the FUSTER PC in 1022SWKT. Check "workstation" box. Password: n400p600
- Open FMRI DATA PROCESSING on the desktop, then open the EXP2006 folder.
- Create a new subject data folder.
    - o Copy and Paste SUBJECT TEMPLATE folder.
    - o Rename folder using first 2 and first 3 letters of first and last name, respectively (FF_LLL).
        - ▪ E.g., subject Mark D. Allen → MA_ALL
    - o Open new subject folder.
        - ▪ Note 6 labeled subfolders for each exam.
        - ▪ Each exam folder contains a subfolder called RAW.
        - ▪ Each RAW folder contains a single file called *FNL.hdr*
- Open *braincoglab.net* icon on desktop, then open the \fMRI DATA subfolder.
- Find and open new subject's folder (yyyymmdd_FF_LLL)
        - ▪ The 8 digit date prefix makes organization on the ftp site easier.
    - o Note 6 labeled subfolders for each exam.
    - o Within each exam folder is a file called *stimulate.sdt* (21.5 MB).
- Copy (click and drag) each *stimulate.sdt* file from each exam folder on braincoglab.net into its corresponding EXAM/RAW folder on FUSTER.
    - o Be very careful! Make extra sure that each file ends up in the correct folder.

- After all 6 raw files are downloaded onto FUSTER,
    - o Change the name of each *stimulate.sdt* file to *FNL.img*
        - ▪ Use upper and lower cases as indicated—this is helpful for later processing steps.

II. CONVERT RAW FILES TO ANALYZE FORMAT

- In each RAW folder, open (double-click) the FNL.img file.
  - o This will launch the MRIcro program.
- The following will appear:
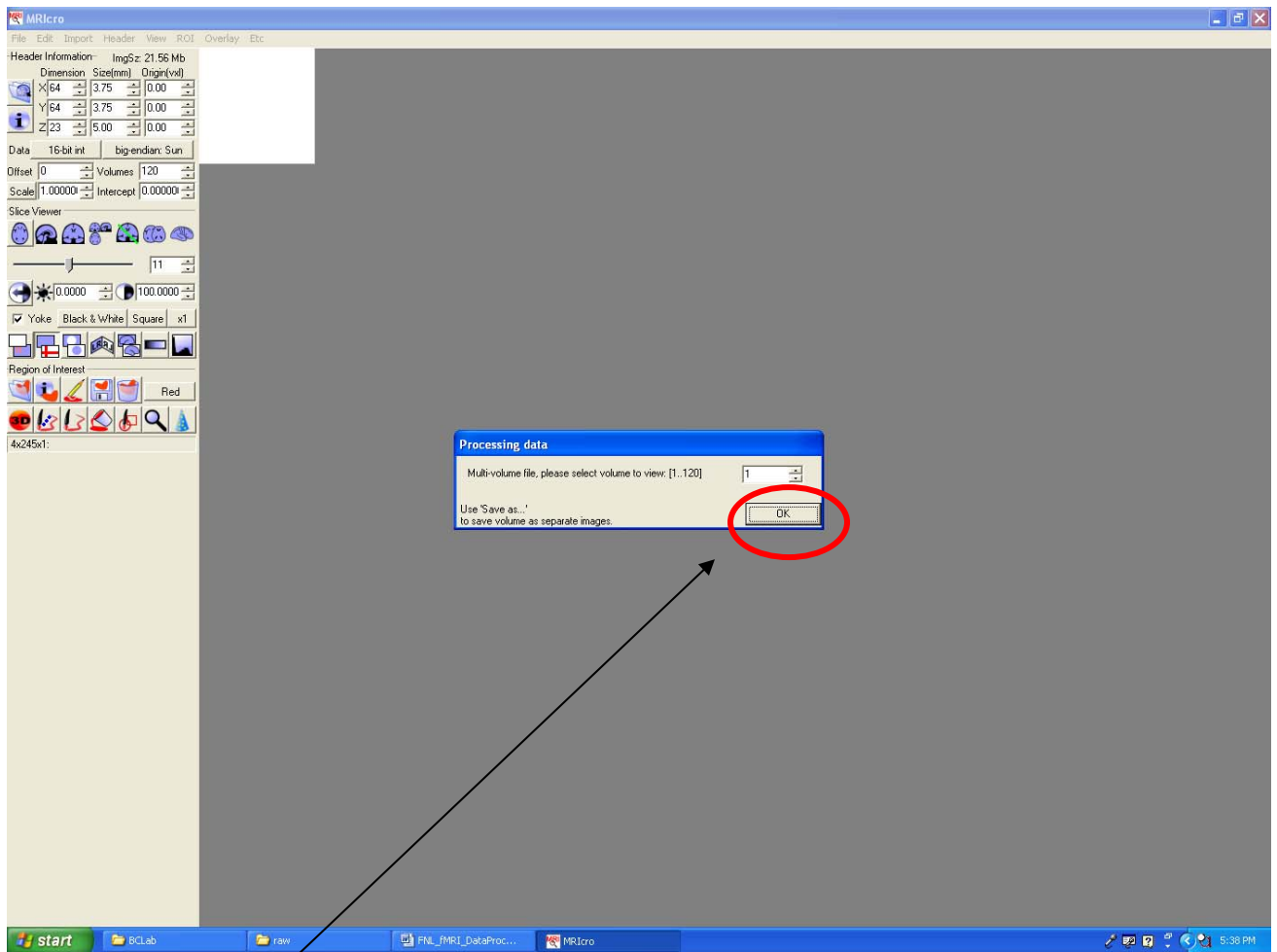
- Click the OK tab
- A single axial slice fMRI image will appear in the white box on the upper-left.

- From the File tab on the upper menu bar, select **Save as … [rotate/clip/format 4D -> 3D]**
  - o See screen-shots below

- Click on the **File** pull-down menu
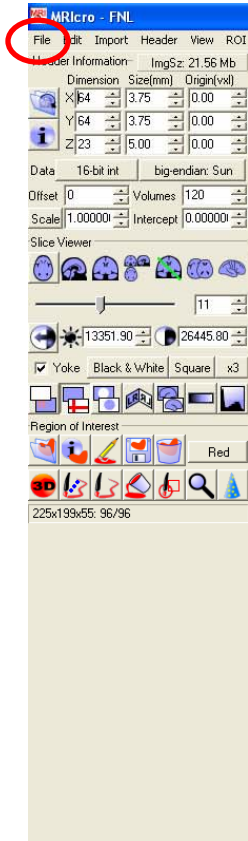
- Select the option **Save as … [rotate/clip/format 4D -> 3D]**
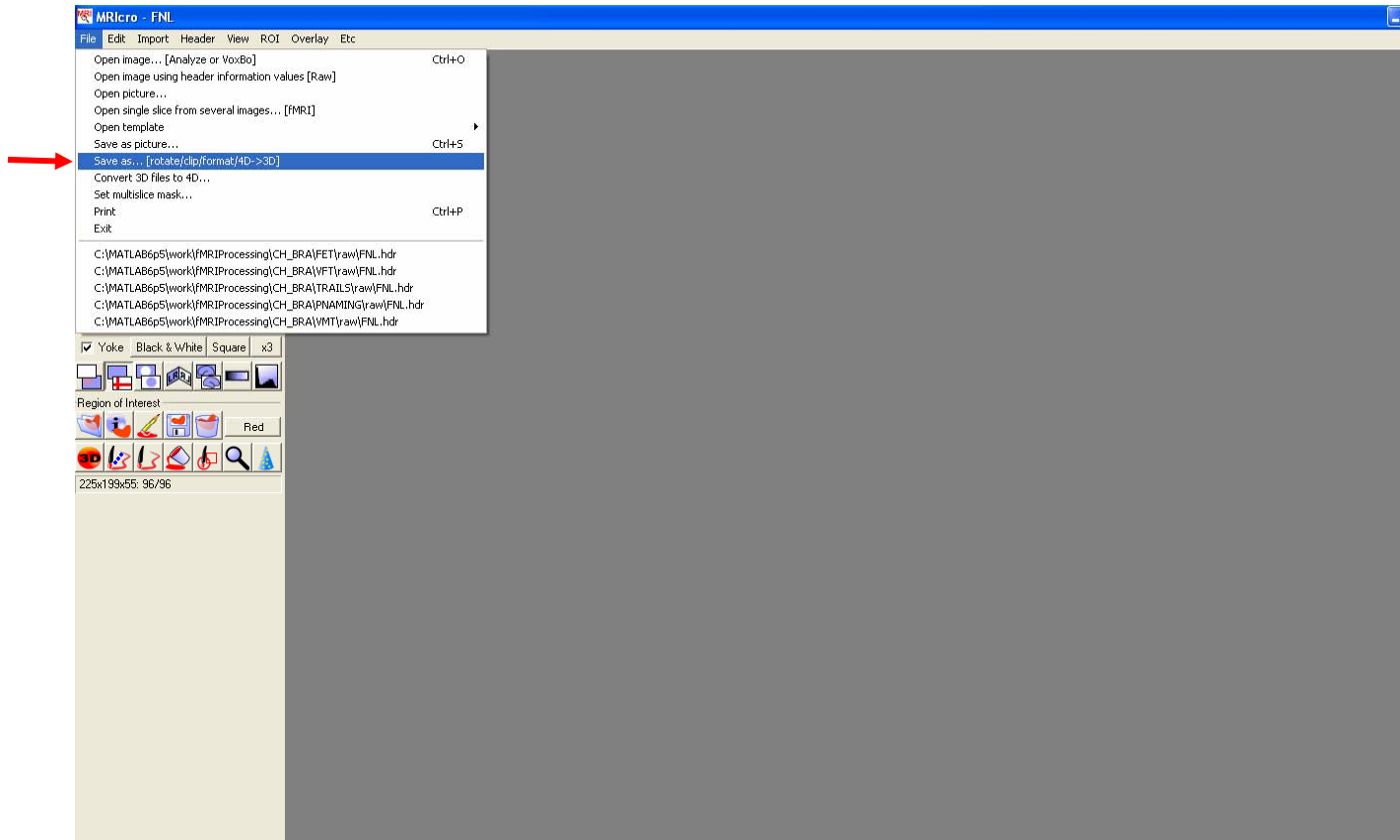
A new dialogue box will appear in the lower left corner.

- Click on the pull-down menu **Axial**
- Select the option **Axial-down**
- Check the box **Flip Left/Right**
- Click **Save [Intel]**

This prompt will appear
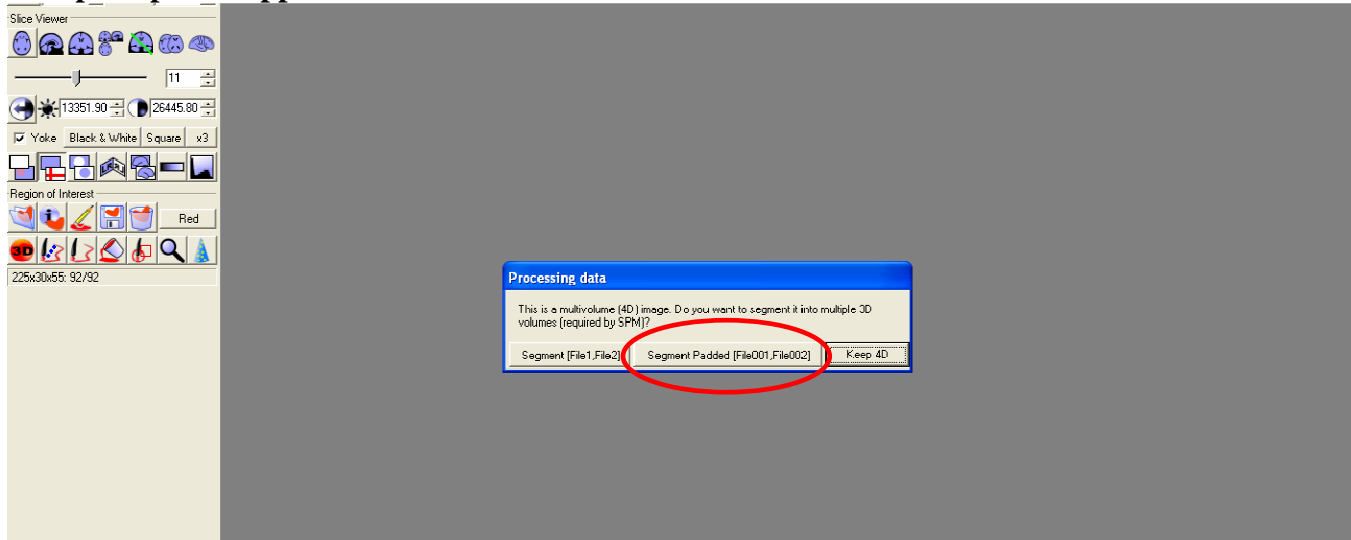
- Select the middle option: **Segment Padded [File 001,File 002]**

A Save Options menu will appear
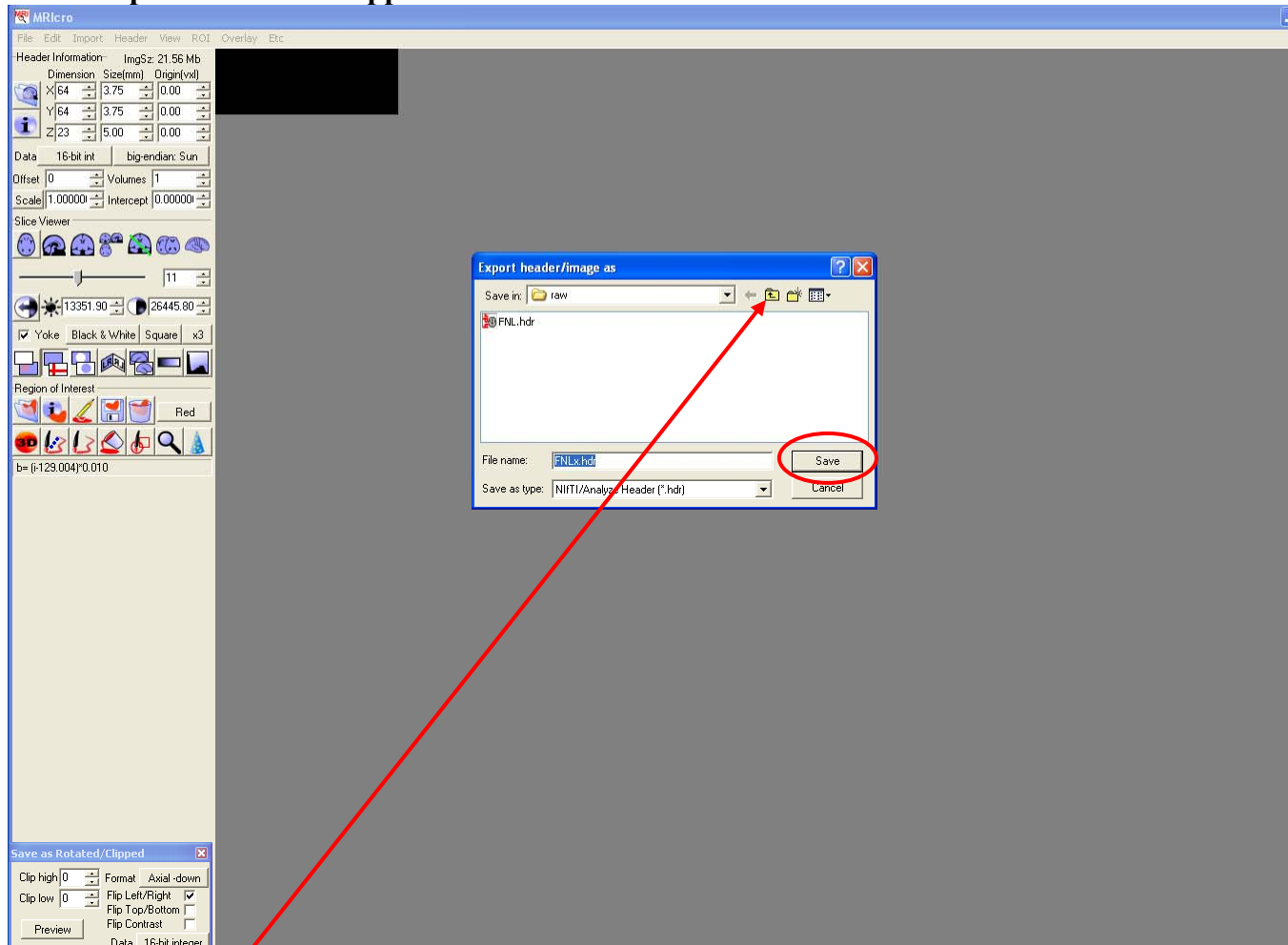
- Move up to the root EXAM folder (e.g., from MATRIX/RAW → MATRIX) by pressing the **Folder-Up** icon.
- Press **Save**.
  - o 120 pairs of Analyze files (FNLx001.hdr, FNLx001.img …) will be written in the root EXAM folder.

- **Repeat this file conversion procedure in the same way for the remaining 5 exams.**

III. DATA PRE-PROCESSING

- Launch Matlab from the desktop icon. The five-panel Matlab window will appear.
- Type **spm fmri** in the command window prompt and press **Enter**
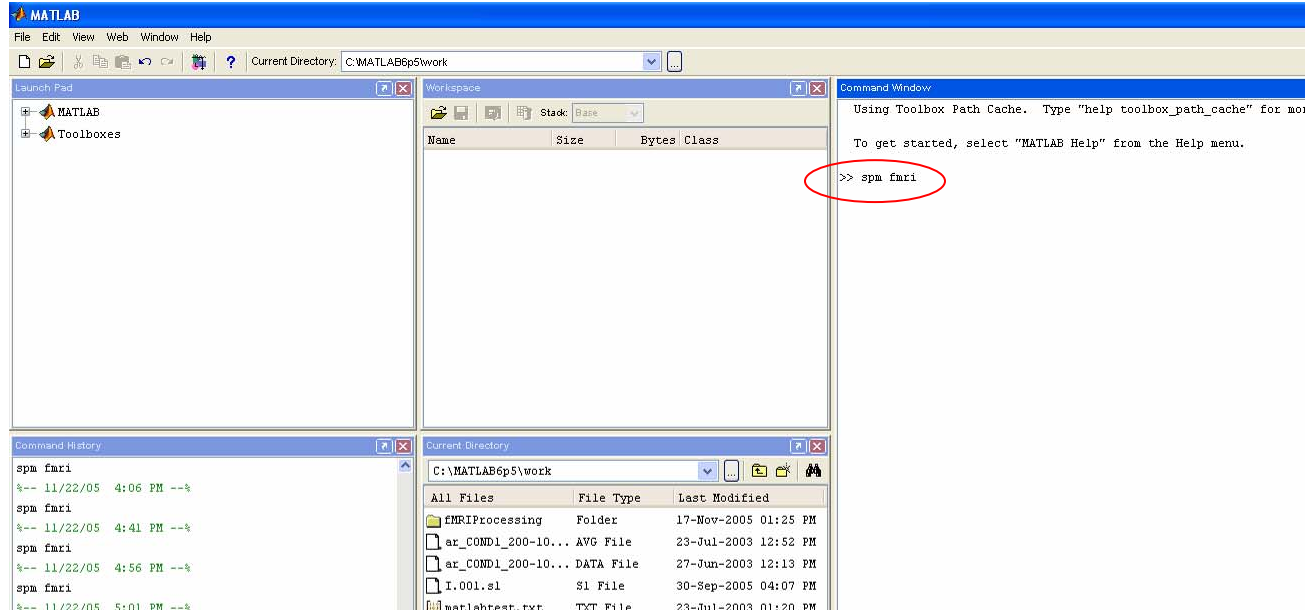
The SPM2 menu windows
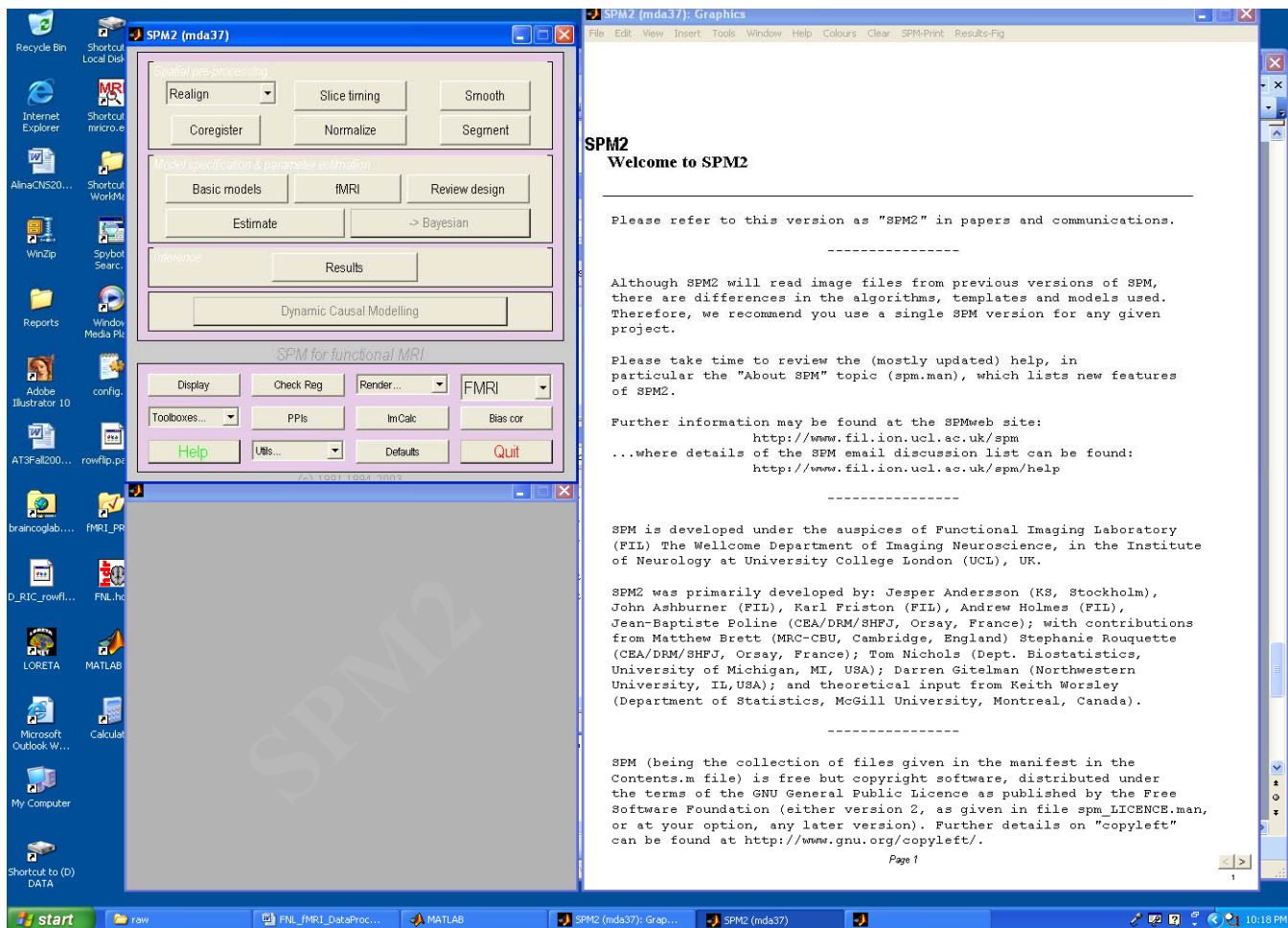
STEP 1: SLICE TIMING CORRECTION

- In the upper left SPM window, press the **Slice timing** button
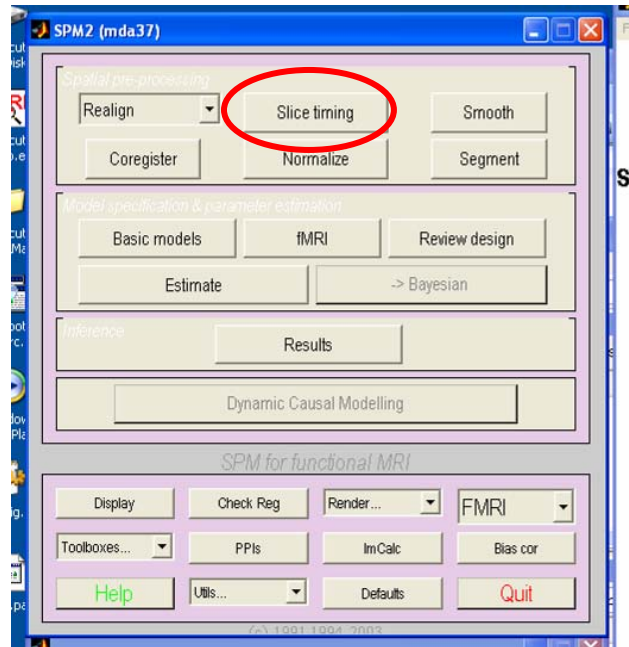
- A prompt will appear that says *Number of Subjects/Session*s with "1" entered in.
    o Press **Enter**

- Next you will be prompted to select the first set of images to be corrected.
    o A Matlab-style *open file* dialogue box will appear with a list of folders in your current directory and two dots at the top of the list.
    o Matlab/SPM uses the following methods for navigating around folders and selecting files:
        ▪ Move into subfolders by single-clicking on the folder name.
        ▪ Move up a directory by single-clicking the *two red dots* at the top of the folder list.
        ▪ Select a file by single-clicking on the file name, and then pressing the **Done** button.
        ▪ When you select a file, it turns blue. To de-select it, single-click it again and it will turn back to black.
- Matlab automatically puts you in a directory called **WORK** when it starts up.
- To get from **WORK** to the first exam files set for timing correction (e.g., MATRIX)
    o Click the two red dots at the top of the current folder list to go up a directory.
    o Then navigate your way to fMRIDATA\\EXP2006**FF_LLL**\\MATRIX
        ▪ **FF_LLL** is the folder name of the subject you are working on
- When you get to the sub-folder \\EXAM (e.g., \\MATRIX)
    o The 120 pairs of .hdr/.img files will appear as a single grouped file (see box below)
        ▪ SPM tries to make life easier this way.
    o Select (single-click) the file set (FNLx*.img).
        ▪ The file set name will turn from black to blue

- Press **Done**

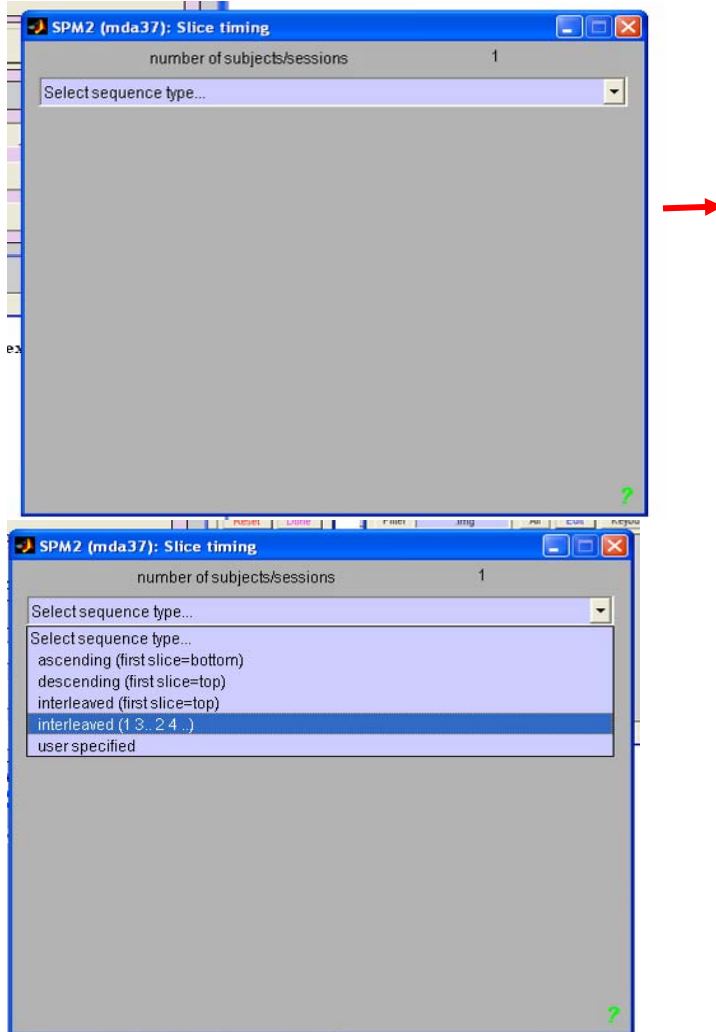**Select file set FNLx*.img (single-click)**   **Press Done**
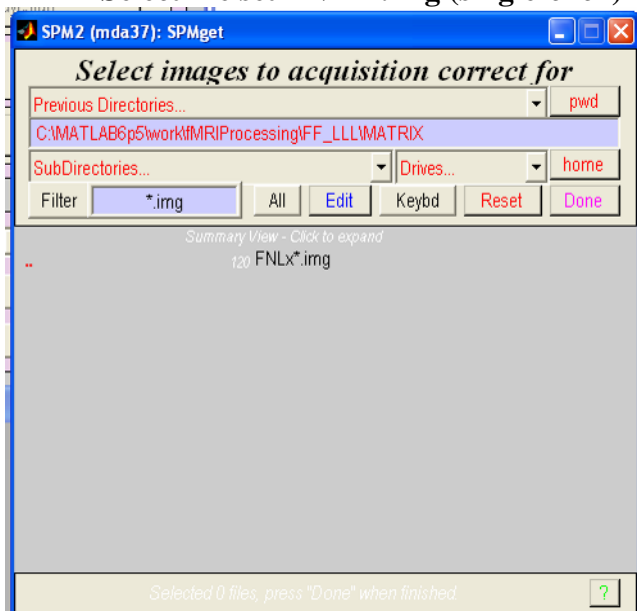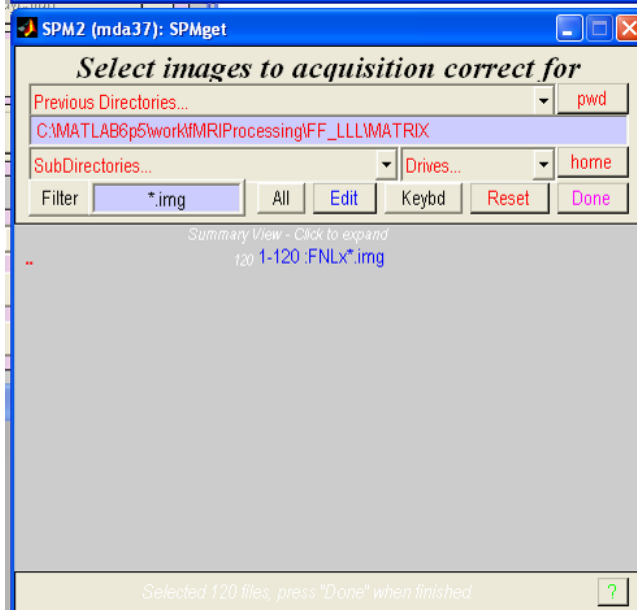
**Next, follow this series of prompts**   **Select option   [interleaved (1 3 .. 2 4..)]**

- Three more prompts will appear with values already filled in:
  - Reference Slice (1=bottom): [11]
  - Interscan interval (TR) {secs}: [2]
  - Acquisition Time (TA) {secs}: [1.913]
    - Just press **Enter** for each one.
- The timing correction routine will then run (takes a few seconds) with a progress bar display.
- Instead of overwriting the original files, timing correction will create a new set of 120 image pairs.
  - The new set will have an "**a**" prefixed to each file (**aFNLx001.hdr, aFNLx001.img**, …)
- Repeat timing-correction for remaining exams.

- ❖ Advanced Batch Option (highly suggested): At the prompt '*Number of Subjects/Session*s', enter **[6]**. SPM will then prompt you to enter in each file set one at a time (press Done after each data set). After the last set is entered, complete the remaining prompt steps as above. SPM will time-correct all 6 exams.
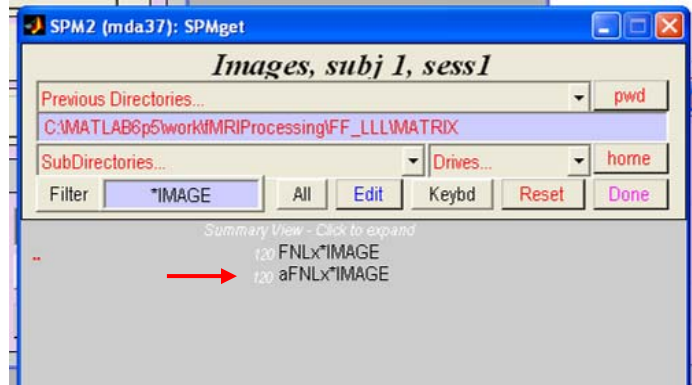
STEP 2: REALIGNMENT AND UNWARPING

Select the **Realign** pull-down menu   Choose option **[Realign & Unwarp]**
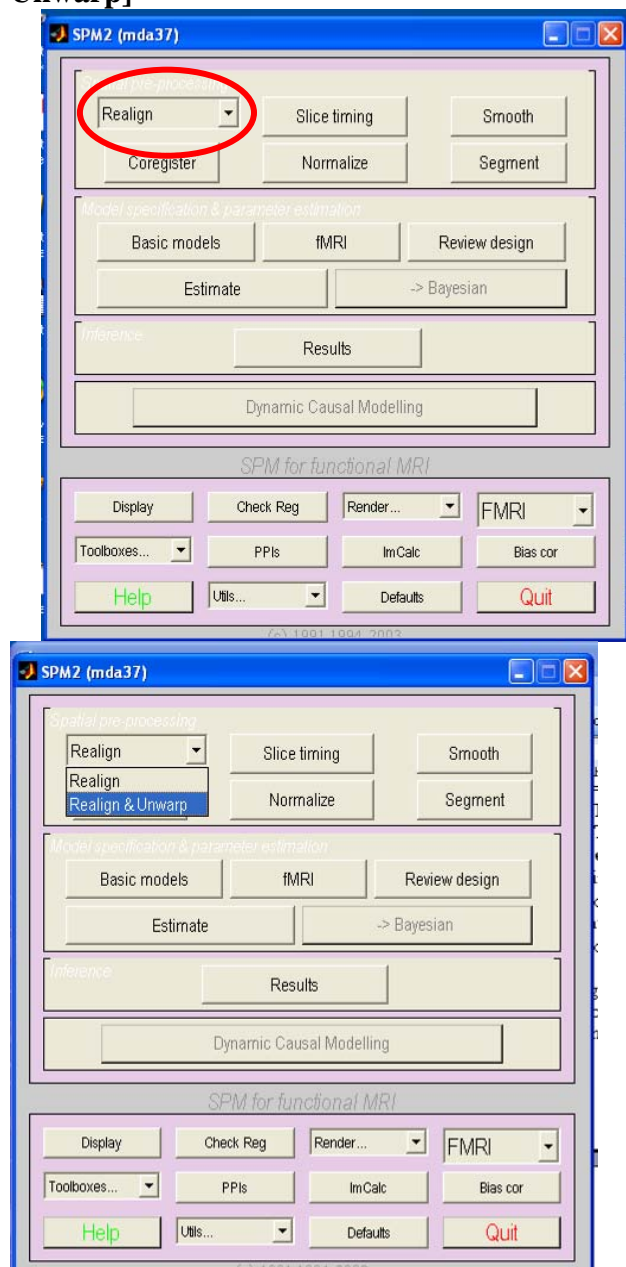

- Press **Enter** for the next two prompts. Default values will appear filled in already:
  - Num subjects: **[1]** *See advanced option below
  - Num session, subj 1: **[1]**

- Select series **aFNLx*.IMAGE**   Press **Done**

- Respond to the next 2 prompts (pull-down menus) as follows:
  - **Model field changes wrt …** → Select ***Pitch & Roll**
  - **Create what?**   → Select **All Images** + **Mean Image**

- The realignment procedure will now run. This can take several minutes.
  - First a progress bar will appear that says "Registering Images"

❖ **Important**: After the *Registering Images* step, a display will appear for 1-2 minutes that shows a record of how much the subject moved during the session (see example of graph below)

After the *Registering Images* step, this display will appear in the Graphics window. It shows how much the subject shifted (top graph), or rotated (bottom graph), his/her head during the scan.

- If any of the 6 lines show that the subject has moved more than **2mm** translation or **2°** rotation, you need to make a note of it—*especially if there are a lot of really large jumps*.
  - Note that this subject has moved less than .4mm and .8° with gradual drift rather than large jumps. This is really good.
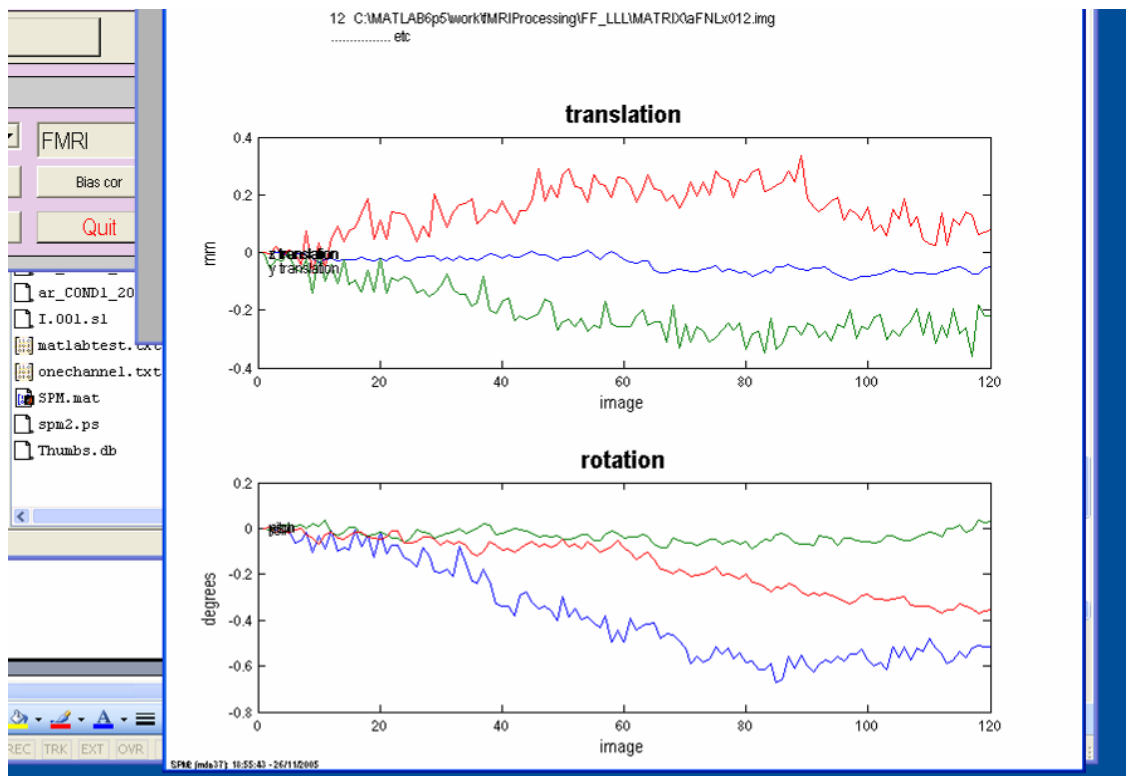
- After a couple of minutes, a few other progress bars and displays will replace this display. So try not to miss it.
  - o If you miss it, there is another (more complicated) way to view these parameters. So don't panic.

- When Realignment/Unwarping finishes, another new set of 120 image pairs will be written in \EXAM.
  - o An additional "**u**" prefix is appended to the new file names to indicate that the files have been time-corrected and realigned/unwarped (**uaFNLx001.hdr, uaFNLx001.img**, …)
- Repeat realign/unwarp for remaining exams.

- ❖ Advanced Batch Option (A little trickier—requires vigilance): Realign/Unwarp can be done batch-style as well. However there are two <u>very</u> important things to keep in mind:
  - o First, at the beginning prompts, enter 6 as the number of *subjects* NOT as the number of *sessions.* That is, you have to treat each exam as though it were a separate subject, with one session per "subject."
    - ▪ **Num subjects: [6]**
    - ▪ **Num session, subj 1: [1]**
  - o Second, you will need to closely monitor the whole process, which will take about 5 minutes, in order to catch the head motion display for each exam.
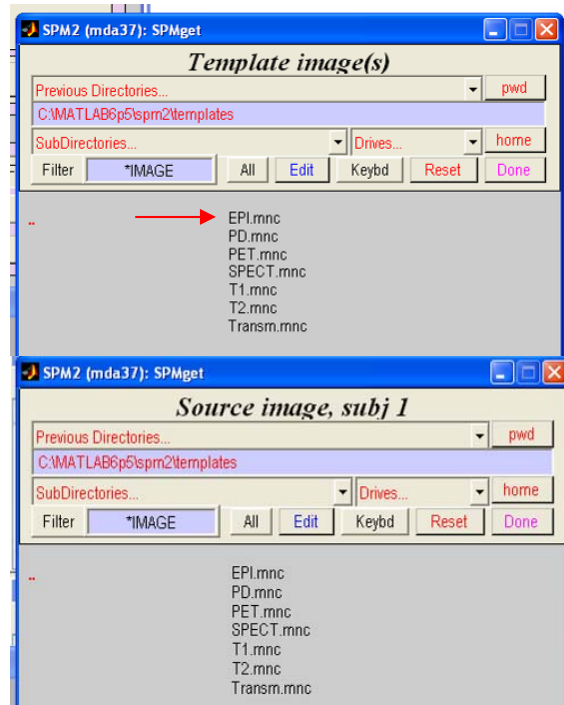
STEP 3: SPATIAL NORMALIZATION

- Select **Normalize** in the SPM control menu
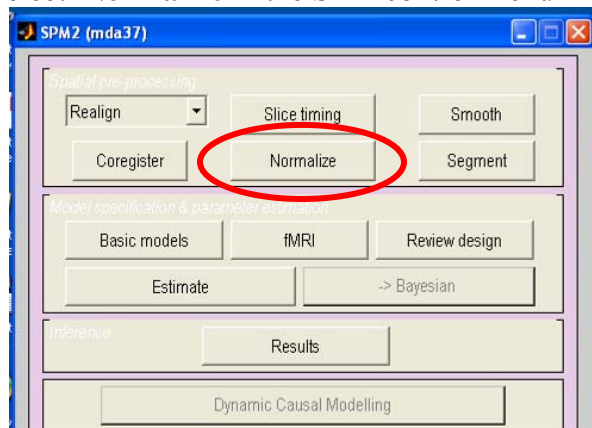
- From the pull down menu **Which Option?** Select: ***Determine Parameters & Write Normalized**
- For the next 2 menu/prompt sequences

1) Select **EPI.mnc,** then press **Done**   2) Click dots twice to move up two directories

- Navigate to the exam folder containing the first data set to be normalized (e.g., \MATRIX)

- o At this point, you will be in C:\MATLAB6p5\spm2**templates**. So you will need to go up 2 directories to C:\MATLAB6p5\ then from there, down 2 directores to \EXP2006\MATRIX
- • When you get to your destination folder:

1. For the prompt **Source Image, subj 1:** Select **meanuaFNLx001.img** then **Done**
2. For **Images to write, subj 1:** Select **meanuaFNLx001.img** then series **uaFNLx*.IMAGE** then **Done**


- • The next prompt will look like the one above on the left, but will say **Source Image, subj 2:**
    - o Option1: Don't select any more data. Just press **Done** again.
        - ▪ SPM will normalize the selected data set.
    - o Option 2; Batch Process the rest of the exam data sets (recommended):
        - ▪ At the prompt **Source Image, subj 2:** Navigate to the folder of the next exam.
            - • Repeat the Source Image selection and Images to Write steps for this data set.
            - • Press **Done**
        - ▪ SPM will continue to prompt you for more "subjects"
            - • After all 6 data sets have been entered,
                - o SPM will prompt for *Source Image, subj 7*
                - o Don't select any more data. Just press **Done**
   - ▪ SPM will normalize all 6 data sets.

- After normalization a "**w**" prefix is appended to the new files to indicate that they have now been time-corrected, realigned/unwarped, and normalized (**wuaFNLx001.hdr, wuaFNLx001.img**, …)

❖ The normalization process will take about 3 minutes (maybe less) for each data set.

<u>STEP 4: SPATIAL SMOOTHING</u>

- ❖ This final step is the easiest and fastest processing step of all.
- Select **Smooth** in the SPM control menu
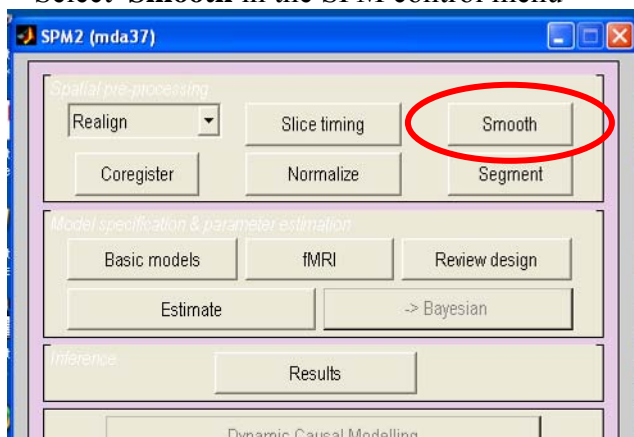
- A prompt will appear that says **Smoothing (FWHM in mm): [   ]**
  - o Type **[8 8 8],** three 8s separated by sinlge spaces in the window and press Enter.

- Next, select the scans to be smoothed
  - o Single-click on the file set **wuaFNLx*.IMAGE**
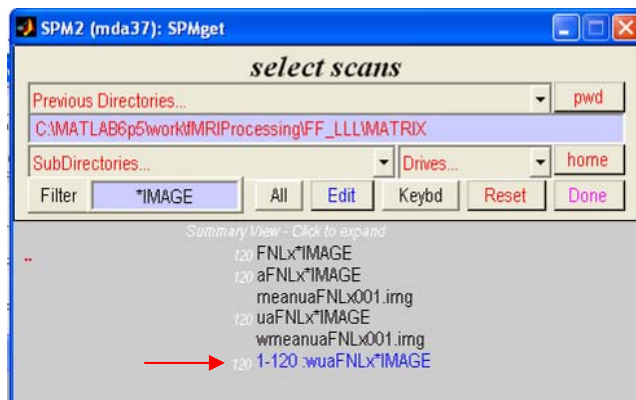
- Option 1: Press **Done**
  - o The selected data set will be smoothed
- Option 2 (very easy): Batch process the remaining exams
  - o Select the first data set, but don't press **Done**
  - o Navigate to the next exam folder, select its **wuaFNLx*** data set
    - ▪ Don't press **Done** yet.
  - o Add the remaining **wuaFNLx*** data sets to the selection list in the same way.
  - o After selecting the last data set, press **Done**

- After smoothing, an "**s**" is added to the prefix string of the new files.

(<u>s</u>wuaFNLx001.hdr, <u>s</u>wuaFNLx001.img, …)

- Now the data are ready to for Level-1 stats analysis
 - o During stats you will deal only with these "**swua"** files.

IV. LEVEL-1 STATISTICAL ANALYSIS

There are three steps in the level-1 statistics procedure:
1. Design Specification
2. Data Specification
3. Parameter Estimation

TO GET STARTED

- Launch Matlab from the desktop icon
    - If Matlab is already running (e.g., from pre-processing) it is a good idea to quit and open it again before running stats (sometimes weird stuff happens if you don't).
        - It is also a good idea to quit and reopen Matlab between stats sessions.
- Before launching SPM from the Matlab prompt, you need to **change the current directory** (i.e., move) to the exam folder of the first data set being analyzed (e.g., \MATRIX).
   - Matlab starts you out in the directory \WORK
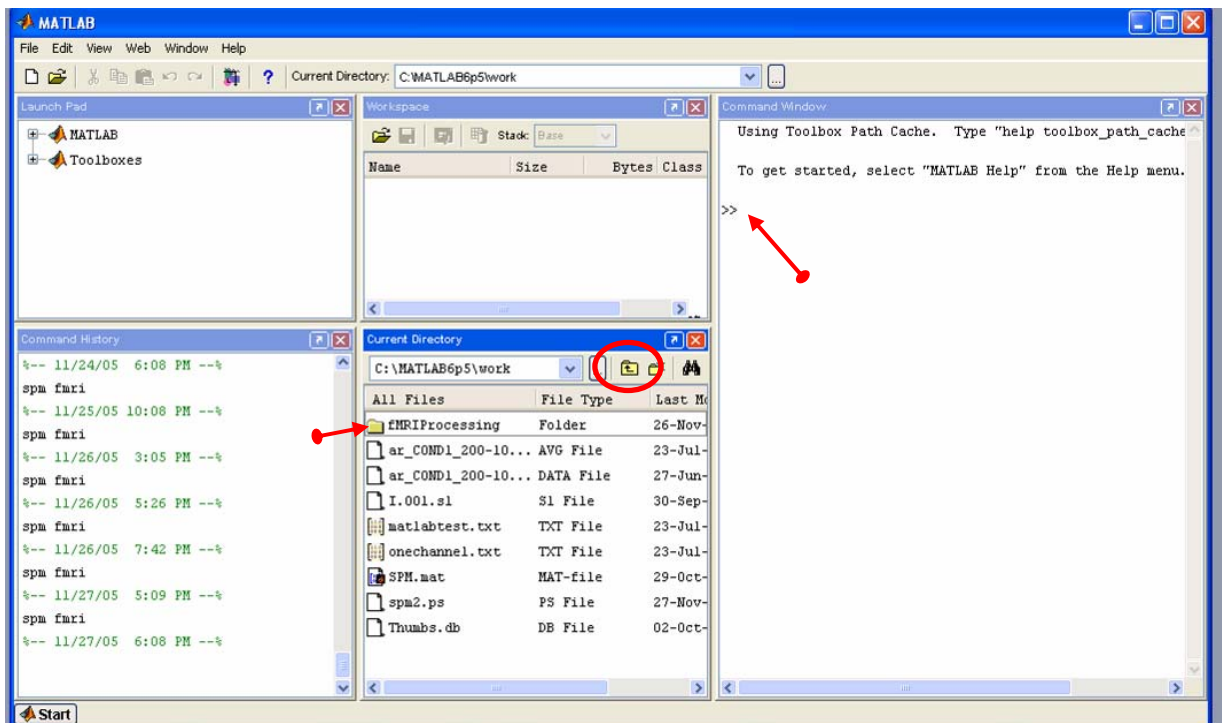
- Use the **lower center** panel to change directories (i.e., move from folder to folder)
    - Single-click on the up-folder icon to move up a directory
    - Double-click on a folder name to move into that folder
- Next, launch SPM2

o Click the cursor on the command prompt in the command window
o Type in **spm fmri** (separated by one space) and press **Enter**
  ✓ *Extreme Lazy Typist Shortcut: Just type "s" then press the up arrow key,*
    • *The rest of the command* **spm fmri** *will auto fill-in.*

STEP 1: DESIGN SPECIFICATION

- Select **fMRI** from the SPM2 control window (upper left panel)
- An options menu window will pop-up just below the control window
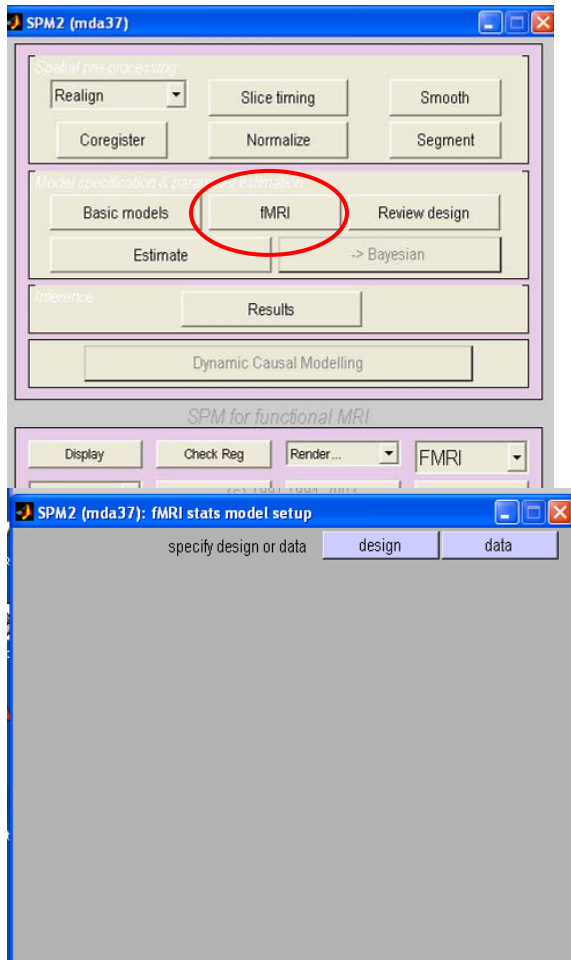 - select **design**
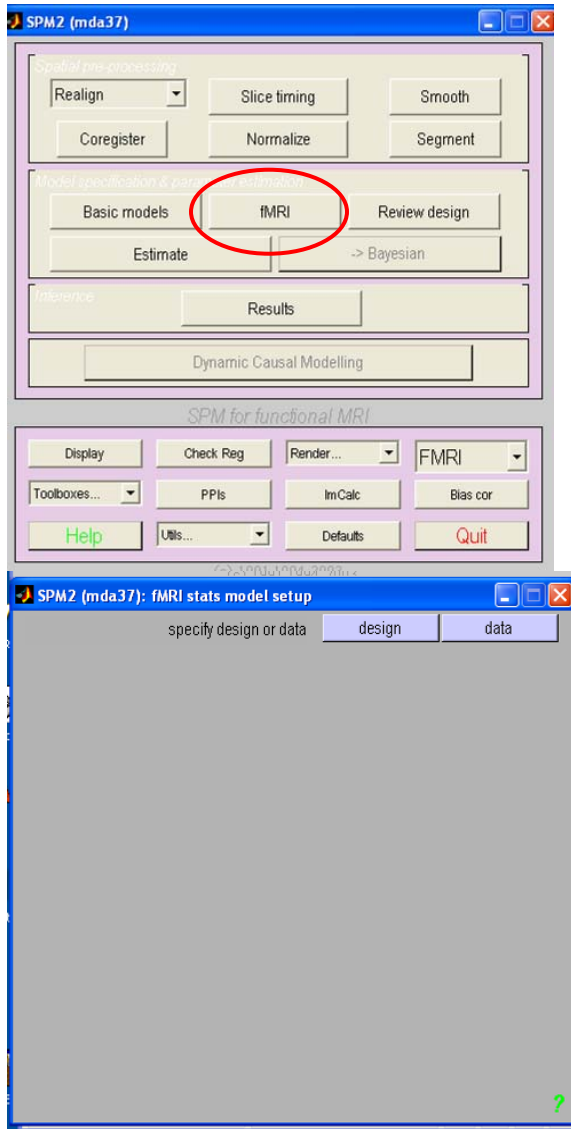
- A series of prompts will then follow.
  - For each one, enter the value or select the option that is indicated in **[ ]**
- **Interscan interval {secs}:**   **[2]**
- **Scans per session:**   **[120]**
- **Specify design in:**   **[scans]**
- **Select basis set:**   **[hrf]**
- **Model interactions:**   **[no]**

- **Number conditions/trials:** **[1]**   *{PNAMING has two conditions, refer to p.1}
- **Name for condition/trial 1:** **[trial 1]**   *{for PNAMING, trial 1=fruit; trial 2=tools}
- **Vector of onsets-trial 1:**   **[   ]**   *{refer to parameters on p.1 & Appendix }
- **Duration[s]:**   **[   ]**   *{refer to parameters on p.1 & Appendix}
- **Parametric modulation:**   **[none]**
- **Other regressors:**   **[0]**

❖ The design step is now completed.
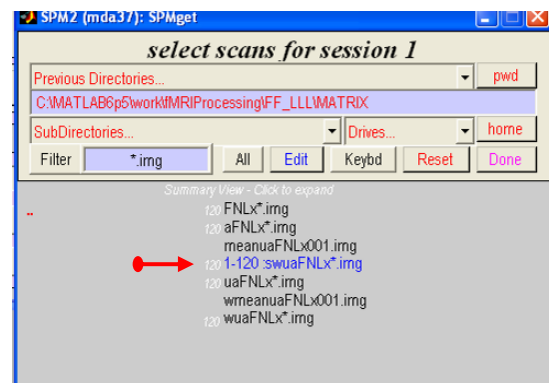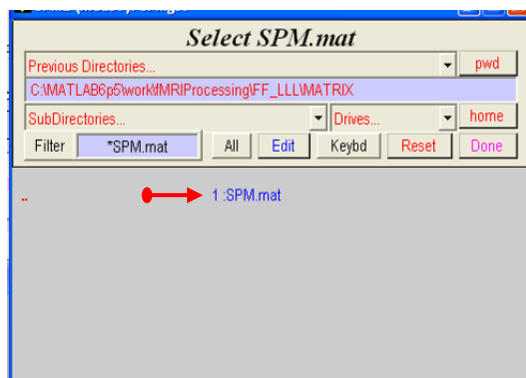 o Several time plots will be displayed in the graphics window—for your amusement only.

<u>STEP 2: DATA SPECIFICATION</u>

- Select **fMRI** (again) from the upper left panel
- Then select **data** from the lower left panel

- Two menu boxes follow:
  - First, select **SPM.mat** -- Press **Done**
  - Next, select series **swuaFNLx*.img** -- Press **Done**

- A series of prompts will then follow.
  - o For each one, enter the value or select the option indicated in **[ ]**
- **Remove Global effects:**   **[none]**
- **High-pass filter:**   **[specify]**
- **Cutoff period (secs):**   **[128]**
- **Correct for serial corr.:**   **[AR(1)]**

- ❖ The data specification step is now completed.
  - o A plot and summary parameters will be displayed in the graphics window

STEP 3: PARAMETER ESTIMATION

- Select **Estimate** from the SPM2 control window (upper left panel)
- When the file selection box appears, select **SPM.mat** -- Press **Done**
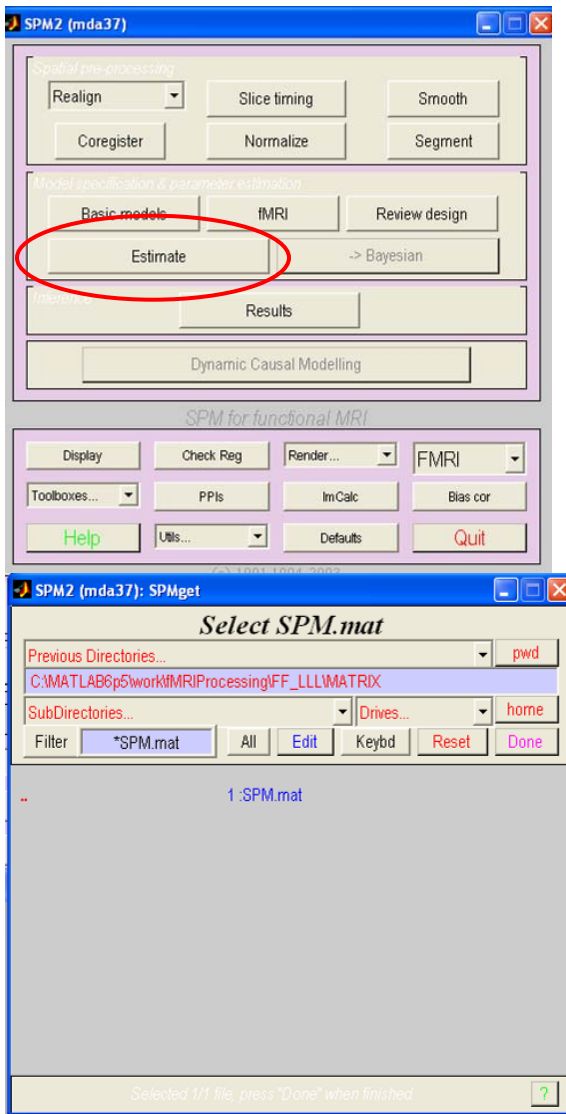
- The parameter estimation program will run for a couple of minutes, showing a couple of progress bars along the way.

- ❖ Level-1 Statistics are now completed.

APPENDIX: TIMING VECTORS

MATRIX
Onset Vector: [*Subject Specific*: Copy and paste from Word file. See below]
Duration Vector: [*Subject Specific*: Copy and paste from Word file]

TRAILS
Onset Vector: [*Subject Specific*: Copy and paste from Word file]
Duration Vector: [*Subject Specific*: Copy and paste from Word file]

PNAMING
Onset Vectors:
  Fruit: [1 25 49 73 97]
  Tools: [13 37 61 85 109]
Duration: 4.5 (for both conditions)

FET
Onset Vector: [1 16 31 46 61 76 91 106]
Duration: 7.5

VMT
Onset Vector: [1 16 31 46 61 76 91 106]
Duration: 9

VFT
Onset Vector: [1 16 31 46 61 76 91 106]
Duration: 9

- Except for MATRIX and TRAILS, all timing parameters are fixed, as indicated above.
- Also, MATRIX and TRAILS have multiple duration values (vectors), instead of a single duration.

- An MSWord file containing onset and duration vectors for MATRIX and TRAILS will be included in each new subject's main folder.
  - During the design stage, open the word file, then you can simply copy and paste each vector from the word file into the appropriate SPM window when prompted to do so.

- PNAMING has two conditions. A duration prompt will appear separately for each condition, after each onset vector prompt. Enter the same value (4.5) for both conditions.