A fMRI study of a cognitive interference task in patients with bulimia nervosa

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A. Abstract

The long-term objective of our research is to use functional MR brain imaging (fMRI) to understand better the neural circuitry involved in impulsive behaviors. The proposed study will be part of our ongoing effort to characterize the similarities and differences of many neuropsychiatric conditions in which impulsivity is a critical part of the pathology. The disorders we are studying include Tourette's syndrome, Obsessive-Compulsive Disorder (OCD), and Attention Deficit Hyperactivity Disorder (ADHD).

We now propose to study patients with a history of Bulimia Nervosa (BN) using the same experiments we have used in the study of ADHD, OCD and TS patients. BN patients are also plagued by impulsive actions as manifested not only by their binging and purging, but also by the high incidence of drug abuse, shoplifting and suicide in their population [Baum A. 1995],[Fahy 1993]. Furthermore, neuropsychological studies have suggested that the cognitive process of BN patients is impulsive [Kaye, 1995]. Through understanding dysfunction in the circuitry that controls behavioral inhibition we will be better able to design and assess the efficacy of new therapeutics for the impulsivity associated with many disorders.

We aim to image the neural systems involved in behavioral inhibition in normal subjects and subjects who have a history of BN. We propose to image the patients as they perform the Simon Spatial Compatibility Task in order to isolate the brain activity specifically associated with impulse control. In this task we present leftward- or rightward-pointing arrows on either side of midline. Subjects are instructed to press a button with either their first or second finger of their right hand to indicate whether the arrow is on the right or left side of the screen. Most (on average 95%) are congruent stimuli (e.g. a right-pointing arrow is shown on the right side of the screen), but incongruent stimuli (e.g. a right-pointing arrow is shown on the left side of the screen) are randomly interspersed among them. Responses to the incongruent stimuli are markedly slow relative to responses to congruent stimuli [Simon, 1967] [Simon, 1969] [Craft, 1970]. The stimulus duration and number are identical to those used in the Stroop, a well-documented interference task. We have previously used this task to show that there are specific fMRl changes associated with the task of responding to incongruent stimuli. An in-press manuscript from our laboratory suggests that the brain regions that are engaged in resolving the interference effects of the incongruent stimuli are similar to those engaged by the Stroop [Peterson, Kane (in press)]. The Simon therefore appears to be a spatial analogue of the Stroop. We prefer to use this task as it will avoid the possible confound posed by reading or language difficulties in patients or subjects.

Our specific aims are: 1) To use fMRI to study the neural activity of 20 bulimic teenagers and adults during the Simon task. 2) To compare the brain activity associated with this task in the BN patients with that of 20 age-matched controls performing the same task. 3) To show that task-related changes in fMRl signal can predict important behavioral measures in our models of impulse control.

B. Titles/Names Of Persons Designated To Obtain Consent

Written informed consent will be obtained for all participants under Yale Human Investigations Protocol #6360, "Natural history, brain structure and function in Tourette's syndrome, obsessive compulsive disorder and Attention Deficit Disorder" (B. Peterson, PI). Persons designated to obtain

informed consent include B. Peterson, Gerianne Alexander, Roxanne Jensen, Amy Basile, Michael Kane, and Ron Whiteman.

C. Research Plan

a. Hypotheses To Be Tested

Our models of impulse control will include fMRI studies of The Simon Spatial Interference Test in 20 patients with Bulimia Nervosa and 20 normal controls. We hypothesize that:

- Normal subjects will demonstrate robust activation in the anterior cingulate, visual association, parietal, and mesial frontal cortices, as well as in the thalamus and basal ganglia. This pattern of activation was demonstrated in our previous studies of the simon and the related interference task the stroop [Delvenne 1997, Roser 1999].

- Subjects who have a history of BN will activate the same brain regions as normal subjects do while performing the interference task. The BN subjects, however, will have larger relative signal changes in these regions after controlling for the effects of age on task-related fMRI signal. In particular we will focus on the anterior cingulate and mesial frontal cortex, which we expect will demonstrate greater activation in the BN group. These group difference will reflect the recruitment of additional executive control resources that are needed to compensate for neural processing inefficiency in the patient groups, which helps them to maintain task performance. The differences will not be explained by another comorbid illness.

The models of functional connectivity developed in normal adults will be independently replicated and validated in normal controls and in patients with a history of bulimia nervosa.

b. Recruitment Methods

Normal controls are recruited from community-based telemarketing lists of households characterized by zip code, age, gender, ethnicity, and income level (Donnelley Marketing, based in Nevada, Iowa; phone 1-800-846-7338). Introductory letters are sent by the investigative team to randomly selected households, with the constraint that the household contains potential subjects with the demographic profile that would match the clinical sample. Because of the difficulties inherent in describing adequately in lay terms, the nature of our study and the safety of the neuroirnaging modality, we first contact by telephone the individual patients to whom we first send the letter of introduction. According to a telephone recruiting script, we explain the purpose and design of our study, allowing them the opportunity to ask any questions they may have about the project. In our 12 years of experience in recruiting for imaging studies, this process of contacting the subjects rather than simply providing a return postcard, has yielded a more normal control population with which our other patient groups can be compared (i.e., we don't have positive responses only from subjects who have some long-standing concern about subtle, undiagnosed disorder). In addition, direct contact with subjects permits us to describe the procedure in greater detail and to answer questions about the procedures that might be foreign to many individuals. Control subjects who are interested in participating in the study are then screened for eligibility by asking if there is any history of psychiatric illness in their family. If the subject meets inclusion criteria for the study, they are invited to visit the psychiatric institute for more detailed information about the study. Using these same recruitment methods in the past, approximately 10% of eligible control families contacted ultimately participate.

BN subjects will be recruited from the records of patients who have been treated at the eating disorder clinic at The Psytchiatric Institute. These individuals have already given their consent to be contacted under IRB protolcol #411 OR. These former patients will also receive an introductory letter and the same scripted phone call as the control patients. In addition the patients will be screened for current symptomatology during the first phone interview. If they are still symptomatic they will be referred to appropriate treatment according to their needs at a site other than Pl.

We have chosen to include only women who are not currently experiencing symptoms of bulimia due to the possibility that there are nutritional state related changes in brain activity during periods of

active binging and purging (ref). To increase our likelihood of recruiting subjects in remission we will recruit patients who were remitted when they left care at The Psychiatric Institute.

All subjects will be women. Our rationale for including only women is that the overwhelming majority (probably more than 90%) of individuals with Bulimia Nervosa are women. Therefore, the inclusion of men with Bulimia Nervosa would be difficult and would have limited relevance to the condition.

Subjects will not be excluded on the basis of minority status, and study samples will reflect the makeup of our clinic population. Our past experience is that approximately 10% of our subjects with Bulimia Nervosa and a similar fraction of controls will be from minority populations (4% African-American, 4% Latina, and 2% Asian-American)

To date, our fIVIRI protocol of the Simon and/ or of the similar task the Stroop has been performed in over 200 patients with TS, OCD or ADHD and over 80 controls. All subjects have tolerated the procedures well. None have withdrawn from the study after enrolling. Although some children and adults have reported mild anticipatory anxiety at the beginning of the IVIRI scan, all have been able to undergo the IVIRI scanning and in fact, when the scan is completed most indicate that the experience was either interesting or enjoyable. We have had no unexpected adverse experiences.

This study has already resulted in several publications (attached), including:

Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC. A functional magnetic resonance imaging study of tic suppression in Tourette's syndrome. Arch Gen Psychiatry, 55: 326-333, 1998.

Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson AW, Gore JC. An fMRI study of Stroop word-color interference: Evidence for cingulate subregions subserving multiple distributed aftentional systems. Biol Psychiatry Priority Communication 45:1237-1258, 1999.

Leung H-C, Skudlarski P, Gatenby JC, Peterson BS, and Gore JC. An event-related fMRI study of color and word interference. Cereb Cortex, 10:552-560, 2000.

Peterson BS, Kane M, Alexander GM, Lacadie C, Skudlarski P, Leung H-C, May J, Gore JC. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. Cognitive Brain Res, in press.

Blumberg HP, Leung H-C, Wexler B, Skudlarski P, Lacadie CM, Anand A, Fredericks C, Harris BC, Charney D, Krystal J, Gore JC, Peterson BS. Prefrontal cortex dysfunction in Bipolar Disorder: an FMRI study. Submitted to Arch Gen Psychiatry.

    c. Study Inclusion and Exclusion Criteria (list in outline form)
- Age 18-45 1. Telephone Screening Questionnaire
- DSM III or IV of BN normal weight type 1. Structured interview w/ trained research
- assistant
- Procedure involving two psychiatrists or Psychologists
- Active eating disorder pathology (restrictive 1. Structured interview w/ trained research
- or binging and purging) assistant
- History of restrictive-type eating disorder 3. Best-Estimate Consensus Diagnostic Procedure involving two psychiatrists or Subjects that are or have been <80% or psychologists
- 120% ideal body weight 4. Weight and height measurements and medical history
- Ferromagnetic implants (e.g. pacemaker, 1. Telephone Screening Questionnaire some penile implants, etc). 2. Standard Metal Screening Questionnaire in the Yale Department of Diagnostics

Inclusion Criteria	
	Radiology (mandatory prior to every MRI scan)
Metal Braces or Retainers	1. Telephone Screening Questionnaire 2. Clinician verbal report
IQ < 85	1. Wechsler Abbreviated Scale of Intelligence (WASI)
DSM-IV Axis I lifetime diagnosis of Pervasive Developmental Disorder, Autism, Asperger's syndrome, a psychotic disorder, or substance dependence	1. Telephone Screening Questionnaire 2. Adult or Kiddie Schedule for Affective Disorders and Schizophrenia (the SADS or Kiddie-SADS) 3. Previous clinician-confirmed diagnosis 4. Best-Estimate Consensus Diagnostic Procedure involving two child psychiatrists
Birth at < 37 weeks gestational age (our prior studies have shown dramatic effects on brain structure and function in prematurely born children)	1. Telephone Screening Questionnaire 2. Questionnaire Assessing Perinatal Risk Factors
History of concussion, seizure disorder, or other neurological illness	1. Telephone Screening Questionnaire 2. Clinician verbal report 3. Clinical Interviews on Study Day
Claustrophobia	1. Telephone Screening Questionnaire 2. Clinician verbal report 3. Clinical Interviews on Study Day

- A prior clinical diagnosis of tics, OCD, or 1 . Telephone Screening Questionnaire ADHD, eating disorders [Bulik 2000],
- Yale Global Tic Severity Scale (YGTSS) affective illness in control subject or the 1st (clinician rating) on Study Day
- degree family members of a potential healthy subject recruit
- BN subjects who have an affective disorder 1. Telephone Screening Questionnaire on the day of the study Adult or Kiddie Schedule for Affective Disorders and Schizophrenia (the SADS or Kiddie-SADS)

D. Study Procedures:
a. Model of Impulse Control
We model impulse control through the suppression automatic response in the Simon task (see introduction). 20 patients with a history of bulimia and 20 age-matched control subjects will perform the simon task during an fMRI scanning session. The subjects will first perform a practice trial to insure they understand the instructions.

b. Event-Related fMRI
We will use event-related fMRI techniques in the study. We will implement a single stimulus version of the Simon word-color interference task. We will timelock the acquisition of images to the presentation of incongruent stimuli. This will allow us to examine the temporal activity of the circuits that subserve impulse control in this task. The signal changes of the fMRI response can be examined at high temporal resolution through the use of averaged single trials. This approach repeats the same trial many times, and the resulting analysis combines imaging data that are acquired at the same time point relative to the stimulus. Although less efficient for localizing activations than 'block' averaging, this approach does allow the temporal intensity profile of individual voxels to be examined with high signal to noise

ratio (SNR) at a temporal resolution on the order of 1 second. As shown in our previous studies of the impulse response of auditory cortex, the onset of transient fMRI signals can potentially be measured to within 100-200 msec, even at this low temporal sampling. The onset and duration of the temporal responses, in addition to amplitude, are parameters of the fMR1 signal that characterize event-related signal changes.

c. Image Acquisition

Head positioning in the magnet will be standardized using the canthomeatal line. Ten axial slices will be acquired to correspond with 10 sections of the Talairach coordinate system [Talairach, 1988]. A T1 -weighted sagittal localizing scan will be used to position the third axial image at the anterior commissure-posterior commissure (AC-PC) line, extending dorsally 8/9ths of the distance to the vertex and 2 slices inferiorly. Slice thickness will be held constant at 7 mm, while the skip between slices will be varied between 0.5 and 2 mm so as to maintain a strict correspondence to the Talairach coordinate system. This prescription of slices provides nearly total brain coverage.

Images will be acquired on a GE Signa 1.5 Tesla scanner (Milwaukee, WI) equipped with echoplanar imaging hardware (Advanced NMR, Inc., Wilmington, MA). Functional images will be obtained with a gradient echo, echo-planar imaging pulse sequence. For all tasks, TR=2000 msec, TE=60, 60 degree flip angle, single excitation per image, 20x4Ocm field of view, a 64x128 matrix, and 3.1x3.1mm in-plane resolution; a total of 300 echoplanar images will be acquired in each slice, providing 100 images per run (25 images per cycle of tic or eye blink suppression and 15 images for each congruent or incongruent block). In addition to these fMRI protocols, we will obtain high resolution anatomical images that will be used to measure regional brain volumes. These scans will include an isotropic voxel 3-D volume MRI scan (sagittal 3D volume SPGR, TR=24, TE=5, 45 degree flip angle, 192x192 matrix, fov=30, nex=2, thickness= 1.2mm, no skip, 124 slices).

d. Subject Characterization

All subjects will complete several self- report questionnaires (listed below). They will also have a structured diagnostic interviews and medical screen. Clinical psychologists or psychiatrists under the supervision of Dr. Walsh will assign DSMIV diagnoses of eating disorders. DSM IV diagnoses of comorbid disorders will be assigned on the basis of a consensus diagnosis procedure, in which Drs. Peterson and Packard review all available information (including all past medical records, school reports, and clinical evaluations) and then independently assign a provisional initial best-estimate diagnosis. disagreements between these 2 raters are then settled through a joint review of the diagnostic materials. In addition, all subjects will undergo neuropsychological testing that includes measures of intelligence, impulse control and sustained attention, and measures of sexually dimolrphic cognitive functions that may also relate to capacities for impulse control. These measures will be used in correlation analyses with measures of regional brain activation. Please see "Instruments" below for a complete listing of these measures and their time requirements.

e. Instruments

Semi-structured clinical interview: Eating Disorders Examination, 1 hour SCID-1, 1 hour YBC-EDS, 40 minutes Yale Global Tic Severity Scale (YGTSS): 10 minutes Yale-Brown Obsessive Compulsive Scale (Y-BOCS): 10 minutes Hamilton Depression Rating Scale (HAM-D) 5-10minutes Hamilton Anxiety Rating Scale (HAM-A) 5-10 minutes

Self-Rating instruments Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS): 40 minutes DuPaul-Barkley ADHD Rating Scale: 2 minutes Edinburgh Handedness Inventory [Oldfield,1971] Self-report measure secondary sex characteristics (Morris & Udry, 1980) Beck Depression Inventory: 3 minutes Body Shape Questionnaire (Cooper, 1987): 5minutes Eating Attitudes Test (Garner and Garfinkel 1979): 5minutes Three Factor Eating Questionnaire (Stunkard and Messick 1985): 5minutes Rosenber Self-Esteem Scale (Rosenberg, 1965): 2 minutes Eating Disorders Examination Questionnaire (Wilson and Smith, 1989): 10minutes

Neuropsychological Evaluation: Wechsler Abbreviated Scale of Intelligence (WASI): 20 minutes Continuous Performance Task: 10 minutes Rotary Pursuit: 8 minutes Mirror Tracing: 10 minutes Stroop Word-Color Interference: 5 minutes Probabilistic Learning Task (Weather Prediction) (Knowlton, Squire,

& Gluck, 1994): 7 minutes Draw-A-Person (Zucker et al., 1983): 5 min Playmate and Playstyle Preferences Structured Interview (Alexander & Hines, 1993) (for children): 8 min Recalled Childhood Gender Identity Scale (for adults) (Zucker et al., 1998): 5 min Two-Dimensional Mental Rotation Task (Collins & Kimura, 1997): 7 min Spatial location (Silverman & Eals, 1992): 5 min Water-Level Task (Tuddenham, 1971): 5 min Reinisch Aggression Inventory (Reinisch, 1981): 12 min
Description of Nonstandard Measures (copies attached):

Rotary Pursuit assesses skill learning. The apparatus (Model 3001 OA, LaFayette Instrument Company) consists of a rotating disk and a metal stylus. The disk rotates at speeds of 15, 30, 45, or 60 rpms while the subject attempts to maintain contact between the metal stylus and a quarter-sized dot on the rotating disk. The task is performed during two blocks of eight trials that are separated by an interval of 30 minutes.

Mirror Tracing is assessed with the Automated Mirror Tracer (Model 58024A, LaFayette Instrument Company), an apparatus consisting of a mirror, a star pattern, and a metal screen. A stylus is used to trace the black star pattern that is hidden by the metal screen, using only the visual feedback that is provided by the mirrored image. The mirror-tracing task is performed during two blocks of five trials that are separated by an interval of 30 minutes.

The Weather Prediction task, a measure of probablistic learning (Knowlton et al., 1994; Knowlton, Mangels & Squire, 1996). The task is administered on a laptop computer (Book). In the Weather Prediction task, children and adults are required to "guess" whether card-like stimuli mean that the weather will be sunny or whether the cards mean that it will rain. On each of 50 trials, stimuli appear on the left side of the computer screen and subjects are prompted to press a key showing a sun or to press a key showing a rain cloud. Following correct responses, a happy face appears on the right side of the screen and children hear a high tone. Following incorrect responses, a sad face appears on the right side of the screen and children hear a low tone.

Playmate and Play Style Preferences Structured Interview (PPPSI) (modified). The interview measure, developed in previous research (Alexander & Hines, 1993), assesses characteristics of play styles and playmates preferred by children. The stimuli presented in the interview consist of a series of 40 cards (20 by 28 cm) showing a simple drawing of two figures with obvious gender cues depicted along with a toy (e.g., doll, truck) or activity (e.g., play fight, run outside). There are two basic card formats that differ as to whether or not figures and play styles are sex-congruent (i.e., male depicted over a masculine play style) or sex-incongruent (i.e., male depicted over a feminine play style). Typically, boys choose male playmates and masculine play styles, whereas girls choose female playmates and feminine playstyles (Alexander & Hines, 1993).

Recalled Childhood Gender Identity Scale (Zucker et al., 1998). This adult self-report questionnaire consists of 22 questions asking about the gender of preferred playmates, types of preferred play (e.g., cosmetics), admiration of male or female roles, and contentment as boy or girl.

Two-Dimensional Mental Rotation Task (Collins & Kimura, 1997). In this task, a target item is a figure in a random orientation with a small arrow placed directly above it. The arrow represents the hour hand of a clock at 12:00, indicating that the figure is at a 12:00 orientation. The task is to determine what the orientation of the figure would look like at a specified time ranging between 2:00 and 10:00

The Water Level Task (adapted from Tuddenham, 1971) measures knowledge of the physical properties of water in a jar. Participants are asked to draw a line on a jar to represent water level. Ten jars are presented in different orientations. Typically, adults are more accurate than are children and, in both children and adults, males are more accurate than are females.

Draw-A-Person. The Draw-A-Person task is used to measure gender group identification (Machover, 1949; Zucker et al., 1983). Task materials include a black crayon and two sheets of white paper. Typically, children and adults draw figures representing their own sex. However, children with higher frequencies of cross-gender play or with gender dysphoria are more likely than controls to draw figures representing the opposite sex.

Silverman & Eals Location Memory Task (Silverman & Eals, 1994) consists of one stimulus card and two response cards, each depicting a spatial array of common objects. The stimulus card depicts a

spatial array of 27 common objects, including nature-items (i.e., cat, elephant, bird, flower), household-items (i.e., phone, iron, teapot, plant), and work-related items (i.e., briefcase, hat, cane). One response card measuring memory for object identities depicts an array of the original 27 objects in their original locations and 20 added objects. A second response card measuring memory for object location depicts the original 27 Objects, with an exchange between the positions of 7 pairs of objects.

The Reinisch Aggression Inventory (Reinisch, 1981) measures an individual's potential for aggressive behavior. For each of six items, the subject is presented with a brief written description of a situation involving interpersonal conflict and asked to choose a response consistent with what they would do in that situation. Adults are asked to retrospect and respond as they would at 10 years of age. There are four possible responses: verbal aggression, physical aggression, withdrawal, or nonaggressive coping. For each situation, there are six pairs of written forced-choice alternatives representing all possible combinations of responses. Boys and men are more likely than girls and women to report that they would respond with physical aggression (effect size (d) 0.7 - 1.1) (Reinisch, 1981; Reinisch & Sanders, 1986). Sexual maturity. The widely used, validated self-report measure of adolescent development (Morris & Udry, 1980) will measure pubertal status in girls 9-years and older and in boys 10years and older. Line drawings of Tanner staging pictures (I to V) are presented along with a brief written description of the physical changes associated with each stage. Children are asked to indicate which of the five pictures is closest to how they look.

Personnel Performing the Procedures: A research assistant (bachelor's level or higher) who has been trained by Dr. Peterson helps subjects through the scanning procedure with the aid of simple relaxation techniques. A trained MR[technician operates the scanner and ensures subject safety throughout the scan. The self-report interviews are conducted by trained research assistants (bachelor's level or higher). Clinical interviews and medical screens will be performed by a research assistant and an M.D. The subject's neuropsychological testing is performed by trained psychologists (master's level or higher).

E. Risks

The risk to subjects from the proposed morphometrics analyses is negligible.

F. Benefits

Those patients who begin the study and are found to be symptomatic will be refered to the appropriate psychiatric treatment. Otherwise, the proposed analyses are unlikely to benefit any subject directly. It is possible, however, that the findings of this study could add to understanding the genetic and environmental causes of neuropsychiatric disorders, and in that case it could indirectly benefit the participating subjects. The subjects do benefit monetarily from their participation in the study, as they are paid $200 upon completion of the protocol.

G. Confidentiality
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In all records from this study, the names of subjects and their family members will be available only to the team of researchers working on the study. Neither their names, nor any identifying information, will be used in any scientific reports from this study. All the information obtained from the subjects is coded by number and kept in locked confidential files. FIVIRI data from this study will be stored on computers behind firewalls in the laboratories of both John Gore, Ph.D. at Yale (Director of NIVIR Research) and our laboratory at NYSPI. The clinical characterization data will be stored solely in our NYSPI laboratory in locked filing cabinets (the paper copies) or on a password-protected personal computer behind a firewall (electronic copies).

H. References

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