XXX
XXXXXX
Designing Clinical Research: 5-page protocol

Title: Investigation of potential neuroimaging correlates related to frontally-mediated neurocognitive function in severe compulsive hoarding

Investigators: XXXXXX

Abstract:
Our group is currently developing a pilot study using selected phenotypic markers, as assessed through neuropsychological and electrophysiological tests, to examine frontally-mediated neurocognitive function in severe compulsive hoarding (SCH). Frontally-mediated neurocognition has already been implicated as abnormal in SCH, as well as in OCD, a related but distinct disorder. The ultimate goal of this study is to identify intermediate phenotypes of SCH for future genetic studies. Similarly, this proposed study, which is intended to complement the neuropsychological and electrophysiological evaluation of SCH-specific phenotypic markers, will develop a protocol that will use established fMRI-based measures of frontally-mediated neurocognitive function, particularly of executive function and conflict or error monitoring. As the larger pilot study will consider the feasibility of our protocol, recruitment procedures, and research methodology, the proposed study will assume the same considerations, with the additional focus on customizing the evidence-based fMRI measures that are first identified through a comprehensive literature evaluation of neuroimaging studies in hoarding and in OCD, to procedures similar to and tested on a small sampling of those used in the original study. Data will be analyzed for differential brain activation between SCH subjects and healthy matched controls during performance of tasks related to executive function and error monitoring. If this study is successful in identifying testable neurocognitive function abnormalities detectable by fMRI, it will be expanded in future studies to examine these measures as potential intermediate phenotypes for this etiologically and phenotypically complex behavioral syndrome.

Specific Aims:
1) To determine the feasibility of recruiting, enrolling, retaining, and assessing neurocognitive function in study participants (including SCH individuals).
2) To identify neurocognitive markers of SCH, with a specific focus on executive function and response/performance monitoring.
3) To determine the appropriateness of identified differences in neurocognitive function as potential intermediate phenotypes for SCH.

Significance:
Severe compulsive hoarding (SCH) is a common but under-recognized problem that has a lifetime prevalence of 2.3% and represents a profound public health burden [1-3]. SCH is defined as the excessive acquisition of and inability or unwillingness to discard seemingly useless items, causing significant distress or functional impairment, and resulting in living and/or work spaces that are unusable for their intended purposes [3, 4]. Individuals with SCH have high levels of distress and social disruption/maladjustment (low marriage rates, high social anxiety

and withdrawal), and report levels of depression and functional impairment that exceed those of OCD and other anxiety disorders [2].

SCH behaviors are part of a discrete clinical syndrome comprised of additional abnormalities suggestive of frontally-mediated neurocognitive dysfunction [4-6]. In addition to the hallmark symptoms described above for SCH, many individuals with this condition also exhibit indecisiveness, perfectionism, difficulty with categorization, disorganization, procrastination, slowness in task completion, actual or perceived alterations in memory, and difficulty with concentration and attention [4-7]. Decision-making, categorization ability, attention, and speed of information processing are often collectively referred to as the "executive functions" of the brain and are frontally-mediated. Neuropsychological studies, including those from Dr. Mathews' group, as well as functional and structural neuroimaging studies, support the thought that abnormalities in frontally-mediated neurocognition are a prominent feature of SCH. Specifically, these studies implicate regions involved in response selection, decision-making, conflict monitoring, error detection, and focused attention [8, 9].

The purpose of this proposal is to develop and pilot an fMRI protocol to examine differences in regions of brain activation between SCH individuals and healthy matched controls using certain tasks that specifically target areas of executive functioning that have been hypothesized to be abnormal in SCH.

Methods:

Study Design – This is a cross-sectional analytic study. The participants will each be imaged in a single several-hour session during the course of their assessment, which is projected to take several days in all. The neuroimaging data will be gathered during this session; thus this study could not be considered a prospective or retrospective study. Measurements include brain scan response readings taken of each subject while doing a neutral task, and while completing the target task. Two different kinds of comparisons will be made, one between baseline and target response readings, and one between SCH and control participant; therefore, it is an analytic and not a descriptive study. However, this is not a randomized blinded trial, and so is more an observational than an experimental study. Also, there is no treatment or intervention given to participants during the study. It is also not a case-control study because the study sample is drawn based on the predictor variable, not the outcome variable (and predictor and outcome are not necessarily causally related).

Study Participants – This study is part of a larger pilot study intended to identify frontally-mediated neurocognitive measures that will act as good potential intermediate phenotypes for SCH. One of the primary aims of the parent study is the assessment of feasibility in conducting various neuropsychological, electrophysiological, and neuroimaging tests in the target populations (SCH and non-hoarding OCD patients and their unaffected family members). For the purposes of this smaller study, only SCH individuals and healthy matched controls (HMCs) will be evaluated, and these subjects will be chosen from the pool of participants in the larger study. Hence, we will endeavor to choose treatment-naïve SCH patients without any psychiatric comorbidities (such as depression), as our projected sample number is small, between 5-10 SCH individuals, with an equal number of HMCs, relative to the proposed number of 25 SCH participants for the larger study. SCH participants have to be at least 18+ years old and meet at

least two of the following three criteria: 1) a score of ≥ 40 on the Saving Inventory, Revised (SI-R), 2) a score of ≥ 20 on the UCLA Hoarding Symptom Scale (UHSS), and 3) a score of ≥ 12 on the Clutter Image Rating Scale (CIR). Participants with comorbid schizophrenia, mental retardation, known dementia, or any acute medical condition that is known or suspected to affect executive function (EF) will be excluded.

Control participants will be included if they do not meet criteria for SCH or OCD. Those with schizophrenia, mental retardation, dementia, or an acute medical condition known or suspected to affect EF will be excluded, as in the SCH participants. All control participants will be matched to the cases with SCH by age, sex, ethnicity, and handedness. SCH participants will be obtained from referrals from mental health clinics throughout San Francisco, and controls will be obtained from newspaper advertisements distributed throughout San Francisco.

Measurements – Predictor variable: Hoarding behavior, as determined by case or control assignment at study entry. Comorbid mental illnesses, such as depression, may be potential confounders in the study. Even if the SCH participants are screened for these illnesses, they may not display themselves on neuropsychological tests but still affect the brain and its hemodynamic activation patterns in ways that we may not yet know. We are also attempting to choose SCH participants who are treatment-naïve, but this may not be possible given that in our larger parent study this is not an exclusion criteria, and many of our SCH subjects will be referred to us from clinics where they presumably will have been identified as SCH and treated medically. However, this factor may not affect our outcomes as much as we might think, given that previous neuropsychological studies in SCH and OCD have suggested no significant effect of medication status [10-12].

Outcome variables: Hemodynamic response reading of normalized images of the brain, taken while individuals are completing tasks designed to involve executive function. Also, for the feasibility aim of this study, percentage of SCH individuals who completed all tasks, out of those who attempted, and qualitative interviews to better understand the nature of any reluctance or difficulty in the participant's completion of the tasks and fMRI imaging required for this study.

Statistical Issues – Because this is a pilot study designed to test feasibility and lead to preliminary results upon which a larger, more formal study will be based, the sample size has been set at around 5 SCH individuals and 5 HMCs, with up to 10 of each set if funding allows. From this starting point, an effect size can be calculated. I first completed a theoretical exercise to estimate a sample size, to see how this might compare with the actual sample size.

Our hypothesis is that SCH individuals will display differential brain activation patterns on fMRI during completion of executive function-based tasks, from HMCs (two-sided). The null hypothesis therefore states that there will be no difference in brain activation patterns between these two participant groups in this instance. Given that the outcome variable is continuous (brain activation in particular brain regions), and the predictor variable is dichotomous (hoarding vs non-hoarding), we would want to use something similar to a *t* test to analyze our results, even though it will not be as robust for sample sizes under 30. (For small sample sizes such as ours, we would consider using the Wilcoxon rank-sum test as our statistical test, though for the purposes of this thought experiment we will use the *t* test.) Standardized effect size was

calculated from data from the recent study by Tolin et al [7] looking at neural correlates of hoarding behavior in hoarders vs HMCs using fMRI imaging. Results were given in BOLD units (blood oxygen level-dependent), one of the standard indices of brain activation in this imaging modality. The difference between hoarders and controls in the left orbitofrontal cortex, one of the main brain regions we will be focusing on in our pilot study of frontally-mediated cognition, was found to be 5.5 BOLD units, our approximate effect size. Standard error was approximately 1.5 units for n = 12, which makes standard deviation equal to 1.5*sqrt(12), or 5.20. E/S = 1.06. With $\alpha = 0.05$ and $\beta = 0.20$, plugging these ingredients into an online calculator (http://www.quesgen.com/SSMeans.php) will result in a sample size estimate of 14 per group.

Working backwards, with a sample size of 5 per group, standardized effect size (E/S) would be 1.7. With a standard deviation of 5.20, this gives an effect size of 8.84 BOLD units, which is what my pilot study would approximately be able to detect (ie, we would not be powered to detect a smaller effect, or difference in mean outcome between our two groups).

Quality Control:

The protocol for fMRI imaging, processing, and analysis will be as follows:

A general fMRI imaging procedure, including details ensuring subject safety and control for environmental variation, has already been devised. Subjects will be requested to have a normal night's sleep the night before each scan, not to have more than one alcoholic drink, and to abstain from caffeinated beverages within 2 hours prior to the scan. Subjects will be placed in the scanner with head restraint, hearing protection, and an emergency squeeze ball in hand to communicate with the researchers. Prior to each scanning session, subjects will have extensive training to become familiarized with the fMRI tasks. They will then complete any necessary safety questionnaires, remove any metal (such as jewelry), and the researchers will answer any questions the subject may have. They will be positioned in the scanner with attached audio and visual presentation and response indicator equipment. All tasks are programmed using presentation software that is synchronized with the video sync pulse of the computer running the task, and the software will also be able to collect behavioral response information. We will collect heart rate and respiratory measures to use as regressors for analysis of the contribution of physiological noise to variance in our fMRI data, using our magnet compatible, non-invasive ECG and ETCO2 monitoring equipment that will be attached to the subjects.

In our analyses we will investigate and identify potential differences in brain activation between the SCH and HMC groups. This will first require processing of the fMRI images, which will use a hemodynamic response reading of normalized images with background fluctuations eliminated. There will be a baseline reading associated with a neutral task, in which the images taken while each subject is completing a task that involves executive functions will be compared with the images of the same subject completing a similar task that does not involve the executive functions. This comparison will be taken for each individual tested. Readings will be quantified using an arbitrary unit at baseline = 0. Comparisons will also be made between groups (SCH vs. healthy matched control subjects), using analyses of covariance for SCH having greater brain activation (in terms of hemodynamic response) than controls and vice versa. Finally, an index of SCH severity taken from clinical criteria for SCH will be used to correlate severity of SCH and hemodynamic responses during task completion, controlling for baseline response.

Our group has members who are experienced in obtaining, processing, and analyzing fMRI data, so we anticipate being able to manage any safety and quality control concerns. fMRI is a relatively safe imaging modality, and we feel there are no major ethical issues we have not addressed. We already have CHR approval and an informed consent form built in to the parent study. We project that the proposed pilot study will take approximately 12 months to complete.

References:

1. Samuels, J., Bienvenu, OJ, Grados, MA, Cullen, B, Riddle, MA, Liang, KY, et al, *Prevalence and correlates of hoarding behavior in a community-based sample.* Behav Res Ther, July 2008. **46**(7): p. 836-844.
2. Frost, R., Steketee, G, Williams, L, *Hoarding: a community health problem.* Health Soc Care Community, July 2000. **8**(4): p. 229-234.
3. Iervolino, A., Perroud, N, Fullana, MA, Guipponi, M, Cherkas, L, Dollier, DA, et al, *Prevalence and heritability of compulsive hoarding: a twin study.* Am J Psychiatry, August 17, 2009.
4. Frost, R., Gross, RC, *The hoarding of possessions.* Behav Res Ther, May 1993. **31**(4): p. 367-381.
5. Grisham, J., Brown, TA, Savage, CR, Steketee, G, Barlow, DH, *Neuropsychological impairment associated with compulsive hoarding.* Behav Res Ther, July 2007. **45**(7): p. 1471-1483.
6. Wincze, J., Steketee, G, Frost, RO, *Categorization in compulsive hoarding.* Behav Res Ther, January 2007. **45**(1): p. 63-72.
7. Tolin, D., Kiehl, KA, Worhunsky, P, Book, GA, Maltby, N, *An exploratory study of the neural mechanisms of decision making in compulsive hoarding.* Psychol Med, May 2008: p. 1-12.
8. An, S., Mataix-Cols, D, Lawrence, NS, Wooderson, S, Giampietro, V, Speckens, A, et al, *To discard or not to discard: the neural basis of hoarding symptoms in obsessive-compulsive disorder.* Mol Psychiatry, January 8, 2008.
9. Gilbert, A., et al., *Brain structure and symptom dimension relationships in obsessive-compulsive disorder: a voxel-based morphometry study.* J Affect Disord, July 2008. **109**(1-2): p. 117-126.
10. Simpson, H., Rosen, W, Huppert, JD, Lin, SH, Foa, EB, Liebowitz, MR, *Are there reliable neuropsychological deficits in obsessive-compulsive disorder?* J Psychiatr Res, April 2006. **40**(3): p. 247-257.
11. Mataix-Cols, D., Alonso, P, Pifarre, J, Menchon, JM, Vallejo, J, *Neuropsychological performance in medicated vs. unmedicated patients with obsessive-compulsive disorder.* Psychiatry Res, April 15, 2002. **109**(3): p. 255-264.
12. Kuelz, A., Hohagen, F, Voderholzer, U, *Neuropsychological performance in obsessive-compulsive disorder: a critical review.* Biol Psychol, February 2004. **65**(3): p. 185-236.