See commentary by Zimmerman

Generalizability of Neuroimaging Studies in 5 Common Psychiatric Disorders Based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Carlos Blanco, MD, PhD[a]; Melanie M. Wall, PhD[b,c]; Martin A. Lindquist, PhD[d]; Jorge Mario Rodríguez-Fernández, MD[b]; Silvia Franco, MD[b]; Shuai Wang, PhD[b]; and Mark Olfson, MD, MPH[b,*]

ABSTRACT

Objective: Although neuroimaging studies have an important role in psychiatric nosology and treatment development, little is known about the representativeness of participants in neuroimaging research. We estimated the effects of commonly used study eligibility criteria on the representativeness of neuroimaging research participants in relation to the general population with the psychiatric disorders of interest.

Methods: Common eligibility criteria were applied from 112 published neuroimaging studies of *DSM-IV* nicotine dependence (13 studies), alcohol dependence (12 studies), drug use disorders (13 studies), major depressive disorder (MDD) (37 studies), and posttraumatic stress disorder (PTSD) (36 studies) to representative US samples with these conditions from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (n = 43,093). The analyses were repeated with NESARC respondents with the disorders and substantial psychosocial impairment.

Results: Most NESARC respondents with nicotine dependence (64.1%), alcohol dependence (57.7%), drug use disorders (86.6%), and PTSD (66.9%), though not with MDD (18.2%), would have been excluded by eligibility criteria used in at least half of the relevant neuroimaging studies. Across the diagnostic groups, comorbid psychiatric and general medical conditions resulted in the largest percentages of exclusions. Corresponding analyses limited to respondents with substantial impairment excluded larger percentages with nicotine dependence (77.6%), alcohol dependence (75.8%), drug use disorders (93.5%), and PTSD (76.8%), though not MDD (18.3%).

Conclusions: Neuroimaging studies tend to recruit highly selected samples with the psychiatric disorders of interest that markedly underrepresent individuals with common comorbid conditions. Larger studies with less restrictive eligibility criteria may promote translation of advances in neuroimaging research to populations commonly encountered in clinical practice.

J Clin Psychiatry 2016;77(12):e1618–e1625
dx.doi.org/10.4088/JCP.15m10264

[a]National Institute on Drug Abuse, Rockville, Maryland
[b]Department of Psychiatry, New York State Psychiatric Institute/Columbia University, New York
[c]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York
[d]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
**Corresponding author:* Mark Olfson, MD, MPH, Department of Psychiatry, New York State Psychiatric Institute/Columbia University, 1051 Riverside Dr, New York, NY 10032 (mo49@cumc.columbia.edu).

Increased interest in evidence-based, personalized, and precision medicine[1–3] and the limited efficacy of existing psychiatric treatments have stimulated renewed interest in the development of neurobiological-based classifications of mental disorders.[4–6] A better understanding of brain circuitry and how psychiatric symptoms relate to circuitry disruptions could provide a stronger foundation to the search for more effective treatments.[7,8] Over the last few years, brain imaging studies have become valuable tools in the identification of structural and functional abnormalities associated with psychiatric disorders. They are also playing an increasingly important role in shaping psychiatric nosology.[4]

An implicit assumption of neuroimaging studies is that the research participants are representative of the population with the target disorder. If research participants systematically differ from individuals with the target disorder in the general population, the study results may have limited generalizability, have low reliability, lead to a biased conceptualization of the target disorder, and provide a suboptimal basis for developing new treatments.[9] To our knowledge, however, no prior study has examined how well participants in neuroimaging studies represent the disorders as they occur in the general population.

We sought to address this gap in knowledge by using methods previously developed to evaluate the generalizability of clinical trials.[10–13] We focus on the representativeness of samples of 5 common psychiatric disorders (nicotine dependence, alcohol dependence, drug use disorders, major depressive disorder [MDD], and posttraumatic stress disorder [PTSD]), for which recent meta-analyses[14–16] of neuroimaging are available. As in our studies of clinical trials, we reasoned that the greater the proportion of individuals with the target disorder who would qualify for a study, the greater the generalizability of the study results.

The present study assesses the effect of exclusion criteria commonly applied in neuroimaging studies to a large, nationally representative general population sample, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). For each of the 5 psychiatric disorders, we examined the proportion of cases in the NESARC that would have been eligible if the exclusion study criteria were applied. By this means, we estimated the population generalizability of neuroimaging studies.

Clinical Points

- Neuroimaging studies of psychiatric disorders tend to recruit individuals that are not representative of the population with the disorder.
- Results from existing neuroimaging studies may not fully apply to patients seen in clinical practice

METHODS

Source of Data

Data were drawn from the 2001–2002 NESARC,[17,18] a nationally representative sample of the adult US population conducted by the National Institute on Alcohol Abuse and Alcoholism and (NIAAA). The target population was the civilian noninstitutionalized population, 18 years and older, residing in the United States. The overall survey response rate was 81% (n = 43,093). Diagnoses were made according to the criteria of the *DSM-IV* using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV),[19] a fully structured diagnostic interview designed for experienced interviewers who are not clinicians. The reliability and validity of the AUDADIS-IV, including clinical reappraisal studies conducted by psychiatrists, are well documented in numerous national and international psychometric studies conducted in both clinical and general population studies.[20–22] The research protocol, including informed consent procedures, received full human subjects review and approval from the US Census Bureau and the US Office of Management and Budget.

Neuroimaging Studies Exclusion Criteria

Exclusion criteria commonly applied in neuroimaging studies of treatments for nicotine dependence, alcohol dependence, drug use disorders, MDD, and PTSD were applied to individuals in the NESARC to determine the proportion of individuals from the general population with those disorders that would have been eligible for the neuroimaging studies. We tabulated the exclusion criteria from each study included in 3 recent meta-analyses[14–16] of neuroimaging studies of the target disorders (see Table 1). Two individuals (J.M.R.-F. and S.F.) independently extracted the data from each study ($\kappa = 0.82$). Initial disagreements were resolved by consensus.

The percentage of individuals excluded by current and lifetime psychiatric diagnoses were estimated from data collected by the AUDADIS-IV. Reliability for the diagnoses examined in this report ranged from $\kappa = 0.63$ for PTSD to $\kappa = 0.79$ for drug use disorders.[19,23] In accord with previous research, exclusion criteria based on time frames shorter than a year, such as drug abuse or dependence in the past 6 months, were applied using a 12-month rather than 6-month time frame.[24,25] Similarly, the criterion "significant risk of suicide" was operationalized as a suicide attempt during the past year.[26] Personality disorders were diagnosed using a lifetime frame.[27,28] Presence of 1 or more significant medical conditions in the last year, which had been confirmed by a physician, included diabetes, cirrhosis or other liver disease, angina pectoris, myocardial infarction and other forms of heart disease, stroke, and AIDS.[29,30] Information to approximate whether respondents were taking psychotropic medications or other medications, had a neurologic disorder other than stroke, had a contraindication for magnetic resonance imaging (MRI), or met some other exclusion criteria was not available in the NESARC.

Analysis Plan

We first examined the basic characteristics of the studies, stratified by diagnosis, including the number of participants in each, imaging method, and general exclusion criteria. Next, we determined the percentage of NESARC survey respondents with the target disorder that would have been excluded from each neuroimaging study by applying each study's exclusion criteria. To account for the possibility that individuals might have been excluded by more than 1 criterion, we also calculated the overall percentage of subjects that would have been excluded by simultaneous application of all of the measurable criteria. As a sensitivity analysis, we also examined the proportion of individuals that would have been excluded by applying criteria that were used in at least half of the studies and in at least three-quarters of the studies.

Because individuals with greater impairment may be of particular interest from etiologic, clinical, and public policy perspectives, we repeated our analyses restricting our NESARC samples to individuals with the target disorder who had scores at least 1 SD below the population mean on the 12-Item Short-Form Health Survey, Version 2 (SF-12),[31] a measure of psychosocial impairment that is commonly used in population surveys.[32] All analyses, including point estimates and standard errors, were conducted with SUDAAN[33] to take into account the complex design features of the NESARC.

As a complementary approach, we also applied the exclusion criteria of each individual neuroimaging study and present results on the range (and mean) percentages of the NESARC samples that would have been excluded across the studies, following the method previously described by Zimmerman and colleagues.[34]

RESULTS

Characteristics of Studies

Although there was considerable variability in the sample size of the studies, particularly for studies of alcohol dependence, the mean sample sizes for most disorders was fewer than 20 participants. The most common imaging method was functional MRI (Table 1).

Exclusion Criteria Most Commonly Applied

Across diagnostic categories, the most common exclusion criterion was co-occurrence of other psychiatric disorders,

Table 1. Sample Size, Method, and Exclusion Criteria for Neuroimaging Studies of Psychiatric Disorders

Design Characteristic	Nicotine Dependence (13 studies[a])	Alcohol Dependence (12 studies[a])	Drug Use Disorders (13 studies[a])	MDD (37 studies[b])	PTSD (36 studies[c])
No. of subjects, mean ± SD	19.7 ± 5.8	26.4 ± 27.1	14.5 ± 7.9	18.2 ± 9.0	13.6 ± 5.0
No. (%) of studies using imaging method					
fMRI	10 (76.9)	12 (100)	9 (69.2)	24 (64.9)	22 (61.1)
PET	3 (23.1)	0 (0)	4 (30.8)	9 (24.3)	11 (30.6)
SPECT	0 (0)	0 (0)	0	4 (10.8)	3 (8.3)
Exclusion criterion, no. of studies (%)					
Alcohol abuse or dependence in the past 6 mo	9 (69.2)	NA	7 (53.8)	30 (81.1)	24 (66.7)
Drug use abuse or dependence in the past 6 mo	10 (76.9)	10 (83.3)	NA	32 (86.5)	28 (77.8)
Current MDD	5 (38.5)	11 (91.7)	7 (53.8)	NA	4 (11.1)
Current bipolar I or II disorder	3 (23.1)	11 (91.7)	7 (53.8)	21 (56.8)	9 (25.0)
Current dysthymia	3 (23.1)	11 (91.7)	7 (53.8)	18 (48.6)	7 (19.4)
Current panic disorder	4 (30.8)	11 (91.7)	7 (53.8)	15 (40.5)	6 (16.7)
Current social anxiety disorder	4 (30.8)	11 (91.7)	7 (53.8)	18 (48.6)	7 (19.4)
Current specific phobia	4 (30.8)	11 (91.7)	7 (53.8)	17 (46.0)	5 (13.9)
Current GAD	4 (30.8)	11 (91.7)	7 (53.8)	16 (43.2)	6 (16.7)
Current PTSD	4 (30.8)	11 (91.7)	7 (53.8)	17 (46.0)	NA
Current ADHD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Current psychotic disorder	4 (30.8)	11 (91.7)	7 (53.8)	18 (48.6)	14 (38.9)
Lifetime MDD	4 (30.8)	0 (0)	2 (15.4)	NA	2 (5.6)
Lifetime bipolar I or II disorder	5 (38.5)	0 (0)	2 (15.4)	4 (10.8)	8 (22.2)
Lifetime dysthymia	3 (23.1)	0 (0)	2 (15.4)	0 (0)	3 (8.3)
Lifetime panic disorder	3 (23.1)	0 (0)	2 (15.4)	3 (8.1)	4 (11.1)
Lifetime social anxiety disorder	3 (23.1)	0 (0)	2 (15.4)	3 (8.1)	4 (11.1)
Lifetime specific phobia	3 (23.1)	0 (0)	2 (15.4)	1 (2.7)	4 (11.1)
Lifetime GAD	3 (23.1)	0 (0)	2 (15.4)	1 (2.7)	4 (11.1)
Lifetime PTSD	3 (23.1)	0 (0)	2 (15.4)	1 (2.7)	NA
Lifetime ADHD	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.6)
Lifetime psychotic disorder	5 (38.5)	0 (0)	2 (15.4)	5 (13.5)	9 (25.0)
Any personality disorder	1 (7.7)	1 (8.3)	3 (23.1)	3 (8.1)	3 (8.3)
Significant risk of suicide	0 (0)	3 (25.0)	0 (0)	2 (5.4)	0 (0)
Significant medical conditions (strict)	10 (76.9)	6 (50.0)	10 (76.9)	16 (43.2)	29 (80.6)
Stroke	1 (7.7)	0 (0)	0 (0)	0 (0)	3 (8.3)
Other[d]	5 (38.5)	0 (0)	7 (53.8)	16 (43.2)	6 (16.7)

[a]Refers to reference 14. [b]Refers to reference 15. [c]Refers to reference 16. [d]"Other" includes obesessive-compulsitve disorder, left handedness, electroconvulsive therapy in past 6 months, MRI contraindication, computed tomography or MRI abnormality, mental retardation, any other medication, gambling activities more than 2 a year or more than 2 cups of coffee per day.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, fMRI = functional magnetic resonance imaging, GAD = generalized anxiety disorder, MDD = major depressive disorder, MRI = magnetic resonance imaging, NA = not applicable, PET = positron emission tomography, PTSD = posttraumatic stress disorder, SPECT = single-photon emission computed tomography.

although there were substantial differences in the frequency with which individual exclusion criteria were applied. Studies of MDD and PTSD were more likely to allow comorbidity with other mood and anxiety disorders than studies of drug or alcohol dependence. Drug use disorders were almost always an exclusion criterion in studies of alcohol dependence, whereas the reverse was true in only slightly over 50% of the studies. Although having a serious medical illness or taking psychotropic medication were common exclusion criteria regardless of the target study diagnosis, taking nonpsychotropic medications was rarely an exclusion criterion. Personality disorders were also seldom an exclusion criterion regardless of the target disorder under study (Table 1).

Estimated Percentages Excluded From Studies

The percentage of individuals in the NESARC with the target disorders that would have been excluded by criteria shared by at least half of the studies ranged from 18.2% for MDD to 86.6% for drug use disorders. Application of eligibility criteria used in at least 75% of the studies would still exclude roughly one-third of individuals with alcohol dependence (36.4%) and drug use disorders (37.4%) and an even larger percentage of adults with nicotine dependence (53.9%) and PTSD (63.3%) (Table 2). When individual criteria were considered (not taking into account the "significant medical conditions" criterion), personality disorders resulted in the largest proportion of exclusions across all diagnoses, followed by lifetime specific phobia for the studies of MDD, PTSD, and nicotine dependence (Table 2).

Restriction of individuals with the target disorders to those with SF-12 scores at least 1 SD below the mean of the general population did not have a substantial effect on the pattern of exclusions. However, the proportion of individuals that would have been excluded was higher for most categories in the impairment-restricted sample (Table 3) than in the full sample (Table 2).

When the criteria of each study were applied, there was marked variability in the percentages of subjects that would have been excluded across all 5 disorders: nicotine (mean = 51.4%; range, 0%–75.3%), alcohol (mean = 40.0%; range, 0%–61.0%), drugs (mean = 62.3%; range, 0%–90.0%), MDD (mean = 48.0%; range, 0–81.0%), and PTSD (mean = 51.1%; range, 1.4%–91.5%).

Table 2. Estimated Percentage of Adults With Psychiatric Disorders in the NESARC That Would Have Been Excluded From Brain Imaging Studies by Eligibility Criteria[a]

Variable	Nicotine (n=4,512)	Alcohol (n=3,142)	Drugs (n=748)	MDD (n=2,076)	PTSD (n=1,715)
No. of studies	13	12	13	37	36
Individuals that would have been excluded, %					
Excluded by any criteria	84.8	68.2	94.4	92.6	94.0
Excluded by criteria applied in at least 50% of the studies	64.1	57.7	86.6	18.2	66.9
Excluded by criteria applied in at least 75% of the studies	53.9	36.4	37.8	18.2	63.3
Individual criterion, %					
Alcohol abuse or dependence in the past 6 mo	21.4	100	55.6	15.3	13.2
Drug use abuse or dependence in the past 6 mo (different than the one in the study when applicable)	8.3	13.7	100	6.7	6.9
Current MDD	9.3	9.0	16.0	100	18.9
Current bipolar I or II disorder	9.6	7.9	16.8	0	18.0
Current dysthymia	1.7	0.9	2.1	8.7	4.1
Current panic disorder	7.0	5.1	11.2	11.5	12.4
Current social anxiety disorder	6.1	4.8	10.9	10.8	12.2
Current specific phobia	13.8	9.9	15.5	18.1	24.4
Current GAD	7.8	6.6	12.2	20.6	20.4
Current PTSD	9.1	6.1	12.8	14.8	100
Current ADHD	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Current psychotic disorder	2.1	0.7	2.4	1.4	3.5
Lifetime MDD	21.6	19.5	25.4	100	36.0
Lifetime bipolar I or II disorder	15.7	13.6	25.1	0	25.8
Lifetime dysthymia	6.0	3.7	7.4	18.2	11.2
Lifetime panic disorder	16.0	11.3	21.8	21.3	25.6
Lifetime social anxiety disorder	12.4	10.2	19.1	18.9	20.9
Lifetime specific phobia	24.7	18.1	25.2	31.4	38.8
Lifetime GAD	14.1	10.8	19.6	30.1	32.4
Lifetime PTSD	12.1	8.1	15.8	18.8	100
Lifetime ADHD	NA[b]	NA[b]	NA[b]	NA[b]	12.8
Lifetime psychotic disorder	5.6	3.3	5.5	5.5	9.4
Any personality disorder	38.7	37.7	60.8	41.4	52.7
Significant risk of suicide	9.3	7.9	18.6	24.9	16.9
Significant medical conditions (strict)	28.4	19.9	19.8	33.1	39.1
Stroke	1.2	0.7	0.8	1.1	1.4

[a]Study exclusion criteria not available for prevalence estimation include obsessive-compulsive disorder, more than 2 gambling activities in a year, current psychotropic medication use, other medication use, neurologic conditions, computed tomography or magnetic resonance imaging (MRI) abnormality, MRI contradiction, mental retardation, electroconvulsive therapy in past 6 months (3 months for MDD, nicotine, and PTSD), left handedness, and more than 2 cups of coffee per day.
[b]No study applied this exclusion criterion for this disorder.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAD = generalized anxiety disorder, MDD = major depressive disorder, NA = not applicable, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions, PTSD = posttraumatic stress disorder.

DISCUSSION

We used a method previously developed to quantify the generalizability of participants in clinical trials,[10,12,13] sometimes called the population generalizability estimator, to examine the effect of applying eligibility criteria commonly used in neuroimaging studies to a large nationally representative sample of adults with the target psychiatric disorders. We found that fewer than 1 in 5 individuals with each of the disorders, except MDD, would have been eligible for most neuroimaging studies. Although there was great variability among studies, the results were generally consistent across disorders. With exclusion criteria that were used in at least half of the neuroimaging studies, more than 50% of adults with each of the target disorders, except MDD, would have been excluded from the studies. If the community samples are restricted to those with significant functional impairment, an even greater proportion would have been excluded from the neuroimaging studies.

Because exclusion criteria can substantially decrease the heterogeneity of study samples,[10,35] selection of exclusion criteria can have a powerful influence on the generalizability of study results. Our findings raise questions about the generalizability of neuroimaging results to broader populations. They also have implications for the design of future neuroimaging research. At present, our understanding of brain abnormalities in psychiatric disorders is based on highly selective samples. Neuroimaging studies with more representative samples may offer opportunities for a more thorough understanding of the underlying neurobiology and better inform development of treatments that will be effective in a wider range of people with the target disorders.

To place these findings in the context of prior research, we compared the generalizability estimates of neuroimaging studies with published estimates of the generalizability of clinical trials for the same disorders. Except for alcohol use disorders, the estimated proportion of individuals excluded from neuroimaging studies was larger than the proportion

Table 3. Estimated Percentages of Impairment-Restricted Adults With Psychiatric Disorders in the NESARC That Would Have Been Excluded From Brain Imaging Studies by Eligibility Criteria[a,b]

Variable	Nicotine (n = 1,298)	Alcohol (n = 689)	Drugs (n = 262)	MDD (n = 1,043)	PTSD (n = 756)
No. of studies	13	12	13	37	36
Individuals that would have been excluded, %					
Excluded by any criteria	95.2	84.7	97.0	96.3	98.3
Excluded by criteria applied in at least 50% of the studies	77.6	75.8	93.5	18.3	76.8
Excluded by criteria applied in at least 75% of the studies	68.1	63.5	47.4	18.3	73.9
Individual criterion, %					
Alcohol abuse or dependence in the past 6 mo	24.8	100	55.2	13.8	14.2
Drug use abuse or dependence in the past 6 mo (different than the one in the study when applicable)	12.5	23.7	100	8.7	9.3
Current MDD	20.2	19.0	28.0	100	25.3
Current bipolar I or II disorder	22.0	23.1	28.7	0	29.3
Current dysthymia	4.2	2.2	3.7	13.1	6.6
Current panic disorder	15.7	13.1	20.2	14.4	21.0
Current social anxiety disorder	13.2	10.3	15.6	13.5	19.6
Current specific phobia	20.6	14.8	19.7	20.8	31.0
Current GAD	18.3	17.6	22.7	27.0	33.2
Current PTSD	17.7	13.4	20.5	17.3	100
Current ADHD	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
Current psychotic disorder	5.9	2.2	4.7	2.4	5.8
Lifetime MDD	32.0	30.0	38.3	100	37.8
Lifetime bipolar I or II disorder	28.8	31.5	37.2	0	37.7
Lifetime dysthymia	10.5	7.4	12.0	24.1	14.8
Lifetime panic disorder	27.2	23.3	34.2	23.0	33.9
Lifetime social anxiety disorder	21.5	18.8	29.1	22.8	30.8
Lifetime specific phobia	34.2	27.7	31.2	32.8	47.0
Lifetime GAD	28.8	25.1	35.6	36.4	45.3
Lifetime PTSD	21.5	16.7	23.4	21.8	100
Lifetime ADHD	NA[c]	NA[c]	NA[c]	NA[c]	9.0
Lifetime psychotic disorder	11.7	7.3	9.2	7.7	14.6
Any personality disorder	54.4	61.1	74.3	47.2	61.2
Significant risk of suicide	23.8	22.1	36.0	32.2	28.4
Significant medical conditions (strict)	39.6	27.2	30.5	38.7	48.9
Stroke	2.4	1.4	1.2	1.9	1.9

[a]Study exclusion criteria not available for prevalence estimation include obsessive-compulsive disorder, more than 2 gambling activities in a year, current psychotropic medication use, other medication use, neurologic conditions, computerized tomography or MRI abnormality, MRI contradiction, mental retardation, electroconvulsive therapy in past 6 months (3 months for MDD, nicotine, and PTSD), left handedness, and more than 2 cups of coffee per day.
[b]Limited to adults with total 12-Item Short-Form Health Survey, Version 2, scores that were ≥ 1 SD below general population mean.
[c]No study applied this exclusion criterion.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAD = generalized anxiety disorder, MDD = major depressive disorder, MRI = magnetic resonance imaging, NA = not applicable, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions, PTSD = posttraumatic stress disorder.

of individuals excluded from clinical trials.[10,12,24,35,36] This suggests that findings from neuroimaging studies tend to be less generalizable than findings from clinical trials.

In the design of future neuroimaging studies, it may be useful to consider the effects of candidate eligibility criteria on the likely composition and representativeness of study participants. As in other areas of psychiatric research, restrictive eligibility criteria may be appropriate in early studies of a disorder, whereas greater attention might be given in later stage studies to the representativeness of the study subjects. Although some exclusion criteria are necessary to ensure the safety of the subjects, such as exclusion of pregnant women, or to avoid sources of severe confounding, such as individuals with strokes, stringent eligibility criteria may nevertheless lead to the exclusion of populations with common characteristics in the target population.[7,18,37,38]

Psychiatric comorbidity is common among individuals with psychiatric disorders, especially among those who seek treatment.[39–42] Excluding individuals with common psychiatric comorbidities may lead to the study of "pure" rather than typical subjects with the target disorder, which could limit understanding of the neurocircuitry of the disorder.[11,12] For example, although MDD and generalized anxiety disorder (GAD) are often comorbid,[43] a high percentage of MDD studies excluded individuals with GAD. Because individuals with MDD appear to differ in their patterns of neural activation in response to emotional conflict tasks depending on whether they have comorbid GAD,[44] MDD studies that exclude GAD may provide a biased representation of the circuitry involved in MDD. Similarly, individuals with PTSD have different patterns of neural activation depending on whether they have comorbid MDD.[45,46] Careful consideration should be given to balancing the needs for sample homogeneity to maximize statistical power with sample representativeness that permits generalizability beyond the study sample.

An alternative to the current approach to conducting neuroimaging studies, which often have modest sample

sizes[14–16] due to cost and logistical constraints, would be to support larger studies with fewer exclusion criteria that would allow for broader generalizability. The results of such research would likely be less prone to problems with reproducibility.[47,48] This research strategy would parallel the approach of clinical trials, where initial smaller trials in selected samples are followed by larger, more generalizable multisite effectiveness trials. An important step for the implementation of larger neuroimaging studies would be development of federal funding mechanisms to field larger neuroimaging studies and support analysis by independent investigators. This type of research, which is being adopted in other areas of medical research,[49–52] would substantially increase the statistical power of neuroimaging studies while facilitating evaluation of the influence of exclusion criteria or other potential moderators on study results. The recent development of National Institute of Mental Health data repositories and the recently started Adolescent Brain Cognitive Development (ABCD) study[53] are examples of initiatives that may provide the necessary platforms to yield highly generalizable neuroimaging results.

A complementary approach that is consistent with recent disease conceptualizations involves focusing on broad, underlying, fundamental dimensions of psychopathology. This perspective views individual disorders as specific manifestations of underlying dimensions or combinations of dimensions.[7,54–57] It explicitly recognizes that abnormalities in certain mechanisms are likely to cut across current diagnostic categories and thus explicitly recognizes and addresses the problem of comorbidity.[4–6] These approaches, which have been recently used to model the relationship between common psychiatric disorders and suicide attempts, could be adapted for neuroimaging studies of psychiatric disorders.[58] An important challenge for these new approaches involves developing methods to examine interactions of several dimensions and exploring how simultaneous abnormalities in these mechanisms affect neuroimaging and clinical expression of each abnormality.

The current study has several limitations. First, translating study exclusion criteria into variables from the NESARC required defining variable specifications. Different specifications would have yielded different exclusion estimates. However, the percentage of excluded subjects was high across all criteria specifications. Because applied research criteria vary across studies, our criteria specifications may not represent their application in all neuroimaging studies. By applying criteria that closely represent those used in several studies, however, our results very likely offer a reasonable lower-bound estimate of the effects of the most commonly used criteria on exclusion of nationally representative samples with the target psychiatric disorders. Second, not all studies used all of the eligibility criteria we examined, and thus the overall percentage of excluded individuals in our study may not necessarily represent all individuals excluded from each trial. In addition, some of the exclusion criteria could not be operationalized in the NESARC sample. Furthermore, some studies have reported their main exclusion criteria, rather than the full, detailed set of exclusion criteria that were actually applied. Thus, the actual proportion of community-dwelling adults who would have been excluded from neuroimaging studies most likely exceeds our estimates. Third, it is possible that limiting the sample to adults with the target disorders who seek mental health treatment would have yielded different results. Given that treatment seeking is a complex function of clinical, social, and economic factors,[59] our approach estimates representativeness without regard to these socioeconomic considerations. Furthermore, neuroimaging studies often recruit symptomatic volunteers rather than treatment-seeking individuals.

In conclusion, neuroimaging studies have thus far primarily involved highly selected samples of individuals with common psychiatric disorders, with particular underrepresentation of individuals with common psychiatric comorbidities. Epidemiologic samples can help estimate the prospective representativeness of samples that participate in neuroimaging studies. As the neuroimaging field matures, eligibility criteria should become more broadly inclusive to increase their clinical and sociodemographic resemblance to affected community samples. Excluding large proportions of target populations may result in selection of highly restricted samples of "pure" rather than "typical" patients with the disorder. Alternative approaches to conceptualizing psychopathology paired with innovative funding strategies may accelerate progress in our understanding of the neurobiology of psychiatric disorders by broadening the range of patients included in neuroimaging research.

Submitted: July 24, 2015; accepted January 7, 2016.

Potential conflicts of interest: The authors report no conflicts of interest.

Funding/support: The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and funded, in part, by the Intramural Program, NIAAA, National Institutes of Health (NIH). Work on this article was supported by NIH grants DA019606, MH076051, and MH082773; Agency for Healthcare Research and Quality grant HS02112; and the New York State Psychiatric Institute (Drs Blanco, Olfson, and Wall).

Role of the sponsor: The sponsors had no additional role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclaimer: The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations or agencies or the US government.

REFERENCES

1. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *N Engl J Med*. 2012;366(6):489–491.
2. National Academy of Sciences. *Toward Precision Medicine. Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington, DC: National Academies Press; 2011.
3. National Institute of Mental Health. The National Institute of Mental Health Strategic Plan. 2008. NIMH Web site. http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml. Accessed August 20, 2013.
4. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748–751.
5. Sanislow CA, Pine DS, Quinn KJ, et al. Developing constructs for psychopathology research: research domain criteria. *J Abnorm Psychol*. 2010;119(4):631–639.
6. Cuthbert BN. The RDoC framework: facilitating transition from *ICD/DSM* to dimensional approaches that integrate neuroscience and

psychopathology. *World Psychiatry*. 2014;13(1):28–35.
7. Blanco C, Krueger RF, Hasin DS, et al. Mapping common psychiatric disorders: structure and predictive validity in the national epidemiologic survey on alcohol and related conditions. *JAMA Psychiatry*. 2013;70(2):199–208.
8. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014;171(4):395–397.
9. Falk EB, Hyde LW, Mitchell C, et al. What is a representative brain? Neuroscience meets population science. *Proc Natl Acad Sci U S A*. 2013;110(44):17615–17622.
10. Blanco C, Olfson M, Goodwin RD, et al. Generalizability of clinical trial results for major depression to community samples: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69(8):1276–1280. *10.4088/JCP.v69n0810*
11. Humphreys K, Weingardt KR, Horst D, et al. Prevalence and predictors of research participant eligibility criteria in alcohol treatment outcome studies, 1970-98. *Addiction*. 2005;100(9):1249–1257.
12. Okuda M, Hasin DS, Olfson M, et al. Generalizability of clinical trials for cannabis dependence to community samples. *Drug Alcohol Depend*. 2010;111(1–2):177–181.
13. Hoertel N, Le Strat Y, Blanco C, et al. Generalizability of clinical trial results for generalized anxiety disorder to community samples. *Depress Anxiety*. 2012;29(7):614–620.
14. Chase HW, Eickhoff SB, Laird AR, et al. The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. *Biol Psychiatry*. 2011;70(8):785–793.
15. Hamilton JP, Etkin A, Furman DJ, et al. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *Am J Psychiatry*. 2012;169(7):693–703.
16. Patel R, Spreng RN, Shin LM, et al. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*. 2012;36(9):2130–2142.
17. Grant BF, Moore T, Shepard J, et al. *Source and Accuracy Statement: Wave 1 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)*. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 2003.
18. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61(8):807–816.
19. Grant BF, Dawson DA, Stinson FS, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend*. 2003;71(1):7–16.
20. Grant BF, Harford TC, Dawson DA, et al. The Alcohol Use Disorder and Associated Disabilities Interview schedule (AUDADIS): reliability of alcohol and drug modules in a general population sample. *Drug Alcohol Depend*. 1995;39(1):37–44.
21. Hasin D, Carpenter KM, McCloud S, et al. The alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability of alcohol and drug modules in a clinical sample. *Drug Alcohol Depend*. 1997;44(2–3):133–141.
22. Canino G, Bravo M, Ramírez R, et al. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J Stud Alcohol*. 1999;60(6):790–799.
23. Ruan WJ, Goldstein RB, Chou SP, et al. The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. *Drug Alcohol Depend*. 2008;92(1–3):27–36.
24. Blanco C, Olfson M, Okuda M, et al. Generalizability of clinical trials for alcohol dependence to community samples. *Drug Alcohol Depend*. 2008;98(1–2):123–128.
25. Hoertel N, Le Strat Y, Lavaud P, et al. Generalizability of clinical trial results for bipolar disorder to community samples: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(3):265–270. *10.4088/JCP.12m07935*
26. Hoertel N, López S, Wang S, et al. Generalizability of pharmacological and psychotherapy clinical trial results for borderline personality disorder to community samples. *Pers Disord*. 2015;6(1):81–87.
27. Hasin D, Fenton MC, Skodol A, et al. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Arch Gen Psychiatry*. 2011;68(11):1158–1167.
28. Lopez-Quintero C, Hasin DS, de Los Cobos JP, et al. Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction*. 2011;106(3):657–669.
29. Cabassa LJ, Humensky J, Druss B, et al. Do race, ethnicity, and psychiatric diagnoses matter in the prevalence of multiple chronic medical conditions? *Med Care*. 2013;51(6):540–547.
30. Peters EN, Schwartz RP, Wang S, et al. Psychiatric, psychosocial, and physical health correlates of co-occurring cannabis use disorders and nicotine dependence. *Drug Alcohol Depend*. 2014;134:228–234.
31. Ware J Jr, Kosinski M, Keller SDA. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–233.
32. Rubio JM, Olfson M, Villegas L, et al. Quality of life following remission of mental disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(5):e445–e450. *10.4088/JCP.12m08269*
33. Research Triangle Institute. *Software for Survey Data Analysis (SUDAAN), Version 9.0*. Research Triangle Park, NC: Research Triangle Institute; 2004.
34. Zimmerman M, Chelminski I, Posternak MA. Exclusion criteria used in antidepressant efficacy trials: consistency across studies and representativeness of samples included. *J Nerv Ment Dis*. 2004;192(2):87–94.
35. Franco S, Hoertel N, McMahon K, et al. Generalizability of pharmacologic and psychotherapy clinical trial results for posttraumatic stress disorder to community samples. *J Clin Psychiatry*. 2016;77(8):e975–e981. *10.4088/JCP.15m10060*
36. Le Strat Y, Rehm J, Le Foll B. How generalisable to community samples are clinical trial results for treatment of nicotine dependence: a comparison of common eligibility criteria with respondents of a large representative general population survey. *Tob Control*. 2011;20(5):338–343.
37. Wisniewski SR, Rush AJ, Nierenberg AA, et al. Can phase III trial results of antidepressant medications be generalized to clinical practice? a STAR*D report. *Am J Psychiatry*. 2009;166(5):599–607.
38. Compton WM, Thomas YF, Stinson FS, et al. Prevalence, correlates, disability, and comorbidity of *DSM-IV* drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2007;64(5):566–576.
39. Olfson M, Blanco C, Wang S, et al. National trends in the mental health care of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry*. 2014;71(1):81–90.
40. Iza M, Olfson M, Vermes D, et al. Probability and predictors of first treatment contact for anxiety disorders in the United States: analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2013;74(11):1093–1100. *10.4088/JCP.13m08361*
41. Blanco C, Iza M, Schwartz RP, et al. Probability and predictors of treatment-seeking for prescription opioid use disorders: a national study. *Drug Alcohol Depend*. 2013;131(1–2):143–148.
42. Olfson M, Liu SM, Grant BF, et al. Influence of comorbid mental disorders on time to seeking treatment for major depressive disorder. *Med Care*. 2012;50(3):227–232.
43. Blanco C, Rubio JM, Wall M, et al. The latent structure and comorbidity patterns of generalized anxiety disorder and major depressive disorder: a national study. *Depress Anxiety*. 2014;31(3):214–222.
44. Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *Am J Psychiatry*. 2011;168(9):968–978.
45. Kemp AH, Felmingham K, Das P, et al. Influence of comorbid depression on fear in posttraumatic stress disorder: an fMRI study. *Psychiatry Res*. 2007;155(3):265–269.
46. Lanius RA, Frewen PA, Girotti M, et al. Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: a functional MRI investigation. *Psychiatry Res*. 2007;155(1):45–56.
47. Button KS, Ioannidis JPA, Mokrysz C, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 2013;14(5):365–376.
48. Munafò M, Noble S, Browne WJ, et al. Scientific rigor and the art of motorcycle maintenance. *Nat Biotechnol*. 2014;32(9):871–873.
49. Blazer D. Independent research by early investigators: an underutilized option. *JAMA Psychiatry*. 2014;71(4):357–358.
50. Department of Health and Human Services. Accelerating the pace of drug abuse research using existing data. 2013. National Institutes of Health Web site. http://grants.nih.gov/grants/guide/pa-files/PAR-13-080.html. Accessed April 24, 2014.
51. Leveraging a recovery act resource to accelerate research on neurodevelopment. National Institutes of Health Web site. http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-15-400.html. Accessed April 24, 2014.
52. National Institutes of Health. Request for information: training needs in response to Big Data to Knowledge (BDK2) initiative. National

Institutes of Health Web site. http://grants.nih.gov/grants/guide/notice-files/NOT-HG-13-003.html. Accessed April 24, 2014.
53. Adolescent Brain Cognitive Study of the Collaborative Research on Addiction at NIH. National Institutes of Health Web site. http://addictionresearch.nih.gov/adolescent-brain-cognitive-development-study. Accessed November 24, 2014.
54. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. *Annu Rev Clin Psychol*. 2006;2:111–133.
55. Lahey BB, Van Hulle CA, Singh AL, et al. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Arch Gen Psychiatry*. 2011;68(2):181–189.
56. Kendler KS, Aggen SH, Knudsen GP, et al. The structure of genetic and environmental risk factors for syndromal and subsyndromal common *DSM-IV* axis I and all axis II disorders. *Am J Psychiatry*. 2011;168(1):29–39.
57. Blanco C, Okuda M, Wang S, et al. Testing the drug substitution switching-addictions hypothesis: a prospective study in a nationally representative sample. *JAMA Psychiatry*. 2014;71(11):1246–1253.
58. Hoertel N, Franco S, Wall MM, et al. Mental disorders and risk of suicide attempt: a national prospective study. *Mol Psychiatry*. 2015;20(6):718–726.
59. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *J Health Soc Behav*. 1995;36(1):1–10.