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Review

Searching human brain for mechanisms of psychiatric disorders. Implications for studies on schizophrenia

Sabina Berretta [a,b,c,*], Stephan Heckers [d], Francine M. Benes [b,c,e]

[a] Translational Neuroscience Laboratory, McLean Hospital, 115 Mill St., Belmont, MA 02478, USA
[b] Department of Psychiatry, Harvard Medical School, 25 Shattuck St., Boston, MA 02115, USA
[c] Program in Neuroscience, Harvard Medical School, 25 Shattuck St., Boston, MA 02115, USA
[d] Department of Psychiatry, Vanderbilt University, 161 21st Ave. S., #T1217, Nashville, TN, USA
[e] Program in Structural and Molecular Neuroscience, 115 Mill St., Belmont, MA 02478, USA

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ABSTRACT

In the past 25 years, research on the human brain has been providing a clear path toward understanding the pathophysiology of psychiatric illnesses. The successes that have been accrued are matched by significant difficulties identifying and controlling a large number of potential confounding variables. By systematically and effectively accounting for unwanted variance in data from imaging and postmortem human brain studies, meaningful and reliable information regarding the pathophysiology of human brain disorders can be obtained. This perspective paper focuses on postmortem investigations to discuss some of the most challenging sources of variance, including diagnosis, comorbidity, substance abuse and pharmacological treatment, which confound investigations of the human brain.

1. Introduction

There is no controversy regarding the fundamental role of human brain studies in investigations of the pathophysiology of psychiatric disorders. These illnesses do after all involve changes in cognitive and emotional behaviors, and there is no other organ of the body where such functions receive their primary mediation. Because these disorders are only diagnosable in patients, the human brain becomes by necessity the primary object of investigation. A clear example of the success of this strategy is the involvement of GABAergic interneurons in the pathophysiology of disorders such as schizophrenia, bipolar disorder and autism (Benes et al., 1992; Akbarian et al., 1995; Woo et al., 1998; Lewis et al., 1999; Benes, 2000; Volk et al., 2000; Benes and Berretta, 2001; Cotter et al., 2002; Heckers et al., 2002; Costa et al., 2004; Guidotti et al., 2005; Lewis et al., 2005; Torrey et al., 2005; Akbarian and Huang, 2006; Fatemi et al., 2009; Lawrence et al., 2010; Blatt and Fatemi, 2011; Fatemi et al., 2011; Guidotti et al., 2011) (see also articles included in this Special Issue). The postulated role of the GABA system in schizophrenia, the main focus of this Special Issue, has originated from a variety of technological approaches to the study of the human brain that include both in vivo brain imaging and postmortem investigations of the human brain.

While studies of this type led important breakthroughs in our knowledge and offer great promise for the future, they also present daunting difficulties related in great part to the inherent complexity of psychiatric disorders and the many potential confounding factors. While it is inconceivable for studies on the pathophysiology of schizophrenia and other psychiatric disorders to be undertaken without investigations on the human brain, the challenges these disorders pose can only be met by a highly diverse and complementary array of methodological approaches, ones capable of integrating human studies with investigations of non-human mammalian species and in vitro cell systems. This integration makes it possible for studies of cognition and emotion to be understood within the context of detailed cellular and molecular mechanisms related to neural circuitry. Our understanding of psychiatric disorders critically depends upon the inherent synergy between brain imaging and postmortem studies of the human brain, human genetic investigations, experimental animals and in vitro models, and their ability to reciprocally complement one another with their respective strengths and weaknesses. In this context, it is essential to maintain an open and constructive dialogue regarding the strengths and weaknesses of each of these respective methodologies. The intent of this perspective paper is to stimulate a dialogue that will help to highlight some of the main challenges that studies of the human brain, and postmortem in particular, in psychiatric disorders present to the field of translational neuroscience.

Methodological innovations applied to postmortem investigations on the human brain have in recent years rapidly amplified their

* Corresponding author at: McLean Hospital, Mailstop 149, 115 Mill St., Belmont, MA 02478, USA. Tel.: +1 617 855 3484.
E-mail address: s.berretta@mclean.harvard.edu (S. Berretta).

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potential and usefulness. Increasingly more sophisticated methodological approaches, such as studies of microarray-based genomic integrity, gene expression and methylation, cell level gene and microRNA expression profiling, as well as epigenetics, proteomics, and quantitative high resolution microscopy, hold important promises for progress (English et al., 2011; Horváth et al., 2011; Moreau et al., 2011; Pidsley and Mill, 2011; Benes, 2012; Mitchell et al., 2014). In parallel, attention to a growing number of potential confounding variables, and advances in our understanding of the effects on the brain of systemic physiological and pathological conditions, has contributed to elevate accepted standards. This process is leading toward increasingly more rigorous approaches with regard to diagnostic criteria, comorbidity, effects of pharmacological treatment and drugs of abuse, among many. Far from wishing to push forth one specific approach over others, a discussion of commonly used strategies is intended to encourage an ongoing conversation about valid approaches to the study of postmortem human brain.

Although we focus on human postmortem investigations, it is important to remember that several of the aspects discussed below are also critical to in vivo imaging studies. Both in vivo and postmortem human studies bring to the fore issues related to reliable psychiatric diagnosis, comorbidity, substance abuse, current and past pharmacological treatment and compliance. Each of these issues presents a distinct challenge to both postmortem and brain imaging studies of the brain in relation to psychiatric disorders. For both, it is critical to emphasize the importance of gathering extensive, detailed, information on study subjects. While this task can be particularly challenging for postmortem studies, which rely heavily on medical records and family interviews/questionnaires, the availability of toxicological and neuropathological assessments represents a significant advantage, as discussed in more detail below. The reliance of human postmortem studies on the availability of subject information underlies the importance of modern approaches to brain banking and thoughtful screening of available information. Other important aspects related to human brain studies have been elegantly discussed by other authors (Deep-Soboslay et al., 2011; Harrison, 2011; Horváth et al., 2011; McCullumsmith and Meador-Woodruff, 2011; Tunbridge et al., 2011).

2. Diagnosis

The debate about diagnostic criteria, highlighted during the recent release of the DSM 5, raises important issues relative to categorical versus dimensional diagnostic approaches (Barch et al., 2013; Heckers et al., 2013). These issues are equally important to clinicians and researchers, as they impact on the conceptual framework and design of group comparisons. Clinical presentations do not often fit into categories and may change over time, raising important questions with regard to the nature of a group, such as schizophrenia, and the testing of hypotheses related to this disorder. For instance, should studies on psychosis include all subjects with psychosis independent of a diagnosis of schizophrenia, schizoaffective disorder, psychotic bipolar disorder or other psychotic disorders? Some patients with an initial diagnosis of one psychotic disorder will be reclassified if they are followed for several years (Bromet et al., 2011; Salvatore et al., 2011). Which diagnosis should be considered the best estimate diagnosis at various time points throughout the illness? While the main goal of a specific study will dictate its design in this regard, we expect that evolving diagnostic criteria in psychiatry will continue to shape the conceptual framework of research studies on these disorders. Conversely, pathophysiological findings contribute to our understanding of the relationships between disorders. For instance, abnormalities affecting the GABAergic system have been consistently reported in schizophrenia and bipolar disorder (Lewis et al., 1999; Benes and Berretta, 2001; Blum and Mann, 2002; Heckers et al., 2002; Costa et al., 2007; Gonzalez-Burgos and Lewis, 2008; Guidotti et al., 2011). However, evidence from the hippocampus indicates that the molecular mechanisms underlying these abnormalities may be different in the two disorders (Benes, 2010). Thus, a disruption of intrinsic inhibitory circuits may represent a shared pathological feature, perhaps underlying overlapping clinical domains, and yet resulting from distinct pathophysiological mechanisms.

For the large majority of postmortem studies, the diagnosis is based exclusively on medical records and family questionnaires. The retrospective nature of these diagnoses represents a clear limitation of these studies. However, it is important to consider that medical records obtained for each brain donor contain detailed information on clinical presentation, hospitalizations, prescription drugs and other therapeutic interventions. Importantly, this information often spans the duration of the illness, and thus represents the views of several clinicians at different times. Clinical records, together with extensive family questionnaires providing a wealth of useful information, such as previous use of drugs of abuse, premorbid symptomatology, and status of living, are reviewed by trained psychiatrists following brain donation. Standard toxicological panels (see below) are also obtained and used to evaluate whether drugs of abuse were taken by control and diseased subjects prior to death. Thus, although carried out in absence of the patient, the diagnostic process for postmortem studies takes into account the full course of the illness for each patient, coalescing diagnoses made at different stages of the disorder with information contained in the medical records and provided by the family, in their totality offering a unique diagnostic perspective, a 'bird's-eye' view of the disorder for each subject including changes of its presentation over time. In addition, prospective recruitment of tissue donors, when possible, allows rigorous clinical diagnosis through antemortem clinical assessment. Although this approach presents considerable logistic challenges, it holds great potential to alleviate some of the difficulties related to diagnosis (Deep-Soboslay et al., 2011).

3. Comorbidity

Comorbidity of psychiatric disorders with other brain disorders, as well as systemic disorders, is a potential source of variance and deserves careful consideration. Within the realm of psychiatric disorders, several clinical domains and/or categorical diagnoses often coexist, such as psychosis, anxiety and depression (Dernovsek and Sprah, 2009; Simon, 2009; Cerda et al., 2010; Potuzak et al., 2012; Braga et al., 2013; Pallanti et al., 2013). The variety of psychiatric disorders represented in the large Scottish family carrying a translocation of the Disrupted In Schizophrenia (DISC-1) gene and the substantial overlap of genetic vulnerabilities among several psychiatric disorders further weaken clinical boundaries between psychiatric conditions (Millar et al., 2000; Blackwood et al., 2001; Millar et al., 2001; Smoller, 2013).

Drug addiction, a condition with frequent comorbidity with other psychiatric disorders (Lasser et al., 2000; Conway et al., 2006; Barnett et al., 2007; Katz et al., 2008; National Collaborating Centre, 2011; Wisdom et al., 2011; Chand et al., 2014; Saban et al., 2014) and of particular interest in the context of investigations on the human brain, is discussed below under the "Substance use disorders" section. Several other brain disorders, such as vascular conditions, Alzheimer's disease and Parkinson's disease, may be comorbid particularly in elderly patients and may represent exclusion criteria in studies focusing on psychiatric disorders. Systemic illnesses, such as metabolic, cardiovascular, and inflammatory conditions, are often associated with psychiatric disorders (e.g. Casey et al., 2011; Ferentinos and Dikeos, 2012; Lang and Borgwardt, 2013; Mitchell et al., 2013). Growing evidence points at robust interactions between several of these conditions and disorders such as major depression (Lang and Borgwardt, 2013) and schizophrenia (Casey et al., 2011; Ferentinos and Dikeos, 2012; Mitchell et al., 2013). Notably, large numbers of cytokines/growth factors and hormones involved in systemic conditions also have distinct neural functions, some currently emerging as potential contributors to the pathophysiology of

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