COMMENTARY

Using Our Brains: The Findings, Flaws, and Future of Postmortem Studies of Psychiatric Disorders

Paul J. Harrison

If one accepts that psychiatric disorders are brain disorders, then direct examination of the brain is as integral to their biological study as is the study of bone marrow for a hematologist. However, such studies are rare in this journal: in 1998, only approximately 3% of data articles were based on postmortem brain tissue, and in 2008, the figure was 2%—compared with more than 20% using brain imaging of one modality or another. It is not that postmortem studies are not of interest; the mean number of times they have been cited equals or exceeds the journal average for that year.

This special issue was stimulated by discussion among the editors as to why there are so few postmortem brain papers, and what, if anything, should be done about it. One good reason for their rarity is, of course, that biological psychiatry is a broad church—increasingly so—and a wide range of approaches and methods are used. There are also insurmountable limits as to what postmortem studies can achieve, of which two in particular stand out. First, they are subject to many confounders and differential confounders (e.g., chronicity of illness, medication, smoking, perimortem factors), which make primary changes intrinsic to the illness hard to distinguish from myriad secondary, compensatory, and epiphenomenal effects. Second, by their nature, results are ultimately descriptive and correlational; it is not possible to manipulate or perturb the brain and measure a response to test hypotheses or probe mechanisms critically. These two factors make it appropriate that only a small proportion of articles in a leading biological psychiatry journal are based on the use of postmortem tissue. However, as in any other field, there are good and bad studies, strengths and weaknesses of the approach, and a mixture of established and controversial findings. The articles in this issue discuss one or more of these topics. The focus is on postmortem studies of psychosis, although the key considerations generalize to other psychiatric disorders.

The first prerequisite is to have brain tissue of suitable quality and quantity. Norms for both parameters have increased substantially over recent years. For example, exclusion of brains with a low pH (because this predicts poor mRNA integrity) has become common and reduces the number of brains available. Over the same period, the average sample size has risen dramatically: in 1991, an early molecular study of schizophrenia in a leading journal had 14 subjects (1), whereas now 150 or more are becoming commonplace (2,3), and a recent study included 400 (4). The trend toward large samples reflects a) a desire to make results more robust, b) studies in which findings are related to genotype (see Kleinman *et al.,* [5]), and c) the inclusion of additional diagnostic categories, for example, addition of a mood disorder group to a "schizophrenia versus control" study, a strategy championed by the Stanley Medical Research Institute (6). Fortunately, the ability to rate and control for brain quality in a molecular sense has improved (see Mccullumsmith and Meador-Woodruff; Tunbridge *et al.* [7,8]), as have the size of brain banks and the quality of their material (see Deep-Solobsay *et al.*) (9). Equally, we should not be complacent about brain collection; it requires sustained funding and dedicated personnel; in many jurisdictions, it has become problematic because of more stringent legal and ethical constraints, and the steep decline in autopsy rates. Further, larger sample sizes, although scientifically beneficial, do come at a considerable cost—financially and otherwise—which may well have contributed to the fewer number of active groups in this field.

On a positive note, over the past decade or so, the range of techniques available and validated for use on postmortem tissue has also increased, broadening the repertoire of studies that are feasible, and their coverage. Most "-omics" technologies can be applied, as illustrated by the reviews by Horvath *et al.* on microarrays (10), English *et al.* on proteomics (11), and Pidsley and Mill on epigenomics (12). There have also been conceptual advances in the use of postmortem brains: in particular, to study the effect of allelic variation on gene expression and gene function (5). One attraction of the developments summarized in these reviews is the potential to better integrate postmortem studies with animal and cellular models of disease (or of drug effects), a potential that has yet to be fully reached and that can occur in both directions. That is, postmortem data can help prioritize experimental work (e.g., by identifying a gene that is differentially expressed in a human brain disorder and which can then be manipulated in vivo or in vitro to study the underlying mechanisms and consequences); equally, a finding in a model system can drive a postmortem brain study that assesses whether comparable changes occur in the disorder itself. A further advantage of these technical developments is that the full molecular profile of the human brain, in all its complexity, can now be interrogated, from DNA (including epigenetic modifications and somatic mutations), through RNA (including microRNAs and antisense transcripts) to proteins (including trafficking and posttranslational modifications). Integrating results across these domains, as well as between human brains and model systems, can together free postmortem brain studies from many, although not all, of their limitations.

Along with these novel reasons for studying postmortem brains, the original rationale—to search for the neuropathological basis of our syndromally defined disorders—persists. Other than for dementia, this has been a long and largely fruitless task, certainly in terms of identifying diagnostic lesions. Nevertheless, progress has been made, and the review by Dorph-Petersen and Lewis (13) is an authoritative and comprehensive update of the findings for schizophrenia, focusing on stereologic studies and complemented by a valuable guide to the key concepts and methods. A specific question about the neuropathology of psychosis has been whether gliosis is or is not present, because this bears on the developmental versus degenerative nature of the disease process (14). Schnieder and Dwork provide a valuable summary of this perennially topical issue (15).

Returning to the paucity of postmortem papers in the journal, a further possible reason might be that reviewers—and editors—are more critical than in other fields (perhaps reflecting the methodological and conceptual constraints), leading to a higher proportion being rejected. However, insofar as we can ascertain, this does

From the Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, United Kingdom.

Address correspondence to Paul J. Harrison, DM (Oxon), FRCPsych, Neurosciences Building, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, United Kingdom; E-mail: paul.harrison@psych.ox.ac.uk.

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not appear to be the case. Certainly, we remain keen to publish papers using postmortem tissue, and we encourage submissions. Although manuscripts will of course be subject to the same review and decision criteria used for all submissions, we recognize the importance and uniqueness of postmortem studies, despite their limitations. We endeavor to balance these considerations when choosing referees and interpreting their reviews and hope that *Biological Psychiatry* will be seen as the natural home for high-quality, innovative postmortem studies of psychiatric disorders.

Professor Harrison reports receiving honoraria for educational lectures, chairing scientific meetings, or advisory boards in the past 3 years from Bristol-Myers Squibb, Janssen, Merck, Otsuka, Sanofi, and Wyeth.

1. Harrison PJ, McLaughlin D, Kerwin RW (1991): Decreased hippocampal expression of a glutamate receptor gene in schizophrenia. *Lancet* 337: 450–452.
2. Eastwood SL, Walker M, Hyde TM, Kleinman JE, Harrison PJ (2010): The DISC1 Ser704Cys substitution affects centrosomal localisation of its binding partner PCM1 in glia in human brain. *Hum Mol Genet* 19:2487–2496.
3. Bigos KL, Mattay VS, Callicott JH, Straub RE, Vakkalanka B, Kolachana B, *et al.* (2010): Genetic variation in CACNA1C affects brain circuitries related to mental illness. *Arch Gen Psychiatry* 67:939–945.
4. Kao W-T, Wang Y, Kleinman JE, Lipska BK, Hyde TM, Weinberger DR, *et al.* (2010): Common genetic variation in neuregulin 3 (NRG3) influences risk for schizophrenia and impacts NRG3 expression in human brain. *Proc Natl Acad Sci U S A* 107:15613–15618.
5. Kleinman JE, Law AJ, Lipska BK, Hyde TM, Ellis JK, Harrison PJ, *et al.* (2011): Genetic neuropathology of schizophrenia: New approaches to an old question, and new uses for postmortem human brains. *Biol Psychiatry* 69:140–145.
6. Torrey EF, Webster M, Knable M, Johnston N, Yolken RH (2000): The Stanley Foundation Brain Collection and Neuropathology Consortium. *Schizophr Res* 44:151–155.
7. Mccullumsmith RE, Meador-Woodruff JH (2011): Novel approaches to the study of postmortem brain in psychiatric illness: Old limitations and new challenges. *Biol Psychiatry* 69:127–133.
8. Tunbridge EM, Eastwood SL, Harrison PJ (2011): Changed relative to what? Housekeeping genes and normalization strategies in human brain gene expression studies. *Biol Psychiatry* 69:173–179.
9. Deep-Soboslay A, Benes FM, Haroutunian V, Ellis JK, Kleinman JE, Hyde TM (2011): Psychiatric brain banking: Three perspectives on current trends and future directions. *Biol Psychiatry* 69:104–112.
10. Horváth S, Janka Z, Mirnics K (2011): Analyzing schizophrenia by DNA microarrays. *Biol Psychiatry* 69:157–162.
11. English JA, Pennington K, Dunn MJ, Cotter DR (2011): The neuroproteomics of schizophrenia. *Biol Psychiatry* 69:163–172.
12. Pidsley R, Mill J (2011): Epigenetic studies of psychosis: Current findings, methodological approaches, and implications for postmortem research. *Biol Psychiatry* 69:146–156.
13. Dorph-Petersen KA, Lewis DA (2011): Stereological approaches to identifying neuropathology in psychosis. *Biol Psychiatry* 69:113–126.
14. Harrison PJ, Lewis DA, Kleinman JE (2011): Neuropathology of schizophrenia. In: Weinberger DR, Harrison PJ, editors. *Schizophrenia, 3rd edition.* Oxford: Wiley-Blackwell, 372–392.
15. Schnieder TP, Dwork AJ (2011): Searching for neuropathology: Gliosis in schizophrenia. *Biol Psychiatry* 69:134–139.