

Finding the Elusive Psychiatric “Lesion” With 21st-Century Neuroanatomy: A Note of Caution

Daniel R. Weinberger, M.D., Eugenia Radulescu, M.D.

The widespread use of MRI has led to a wealth of structural and functional anatomical findings in patients with diverse psychiatric disorders that may represent insights into pathobiology. However, recent technical reports indicate that data from popular MRI research—particularly structural MRI, resting-state functional MRI, and diffusion tensor imaging—are highly sensitive to common artifacts (e.g., head motion and breathing effects) that may dominate the results. Because these and other important confounders of MRI data (e.g., smoking, body weight, metabolic variations, medical comorbidities, psychoactive drugs, alcohol

use, mental state) tend to vary systematically between patient and control groups, the evidence that findings are neurobiologically meaningful is inconclusive and may represent artifacts or epiphenomena of uncertain value. The authors caution that uncritically accepting from study to study findings that may represent fallacies of all sorts carries the risk of misinforming practitioners and patients about biological abnormalities underlying psychiatric illness.

Am J Psychiatry 2016; 173:27–33; doi: 10.1176/appi.ajp.2015.15060753

“Stop da music...stop da music.”

—Jimmy Durante

At the turn of the 20th century, basic research about psychiatric disorders was focused on the postmortem brain in a search for anatomical differences associated with these conditions. Many findings were reported, but none withstood the test of time and more critical analyses of the subject. Now, as we charge into the 21st century with dramatic new technologies and discoveries about psychiatric disorders, there has been a renaissance of neuroanatomical investigations not based on the postmortem brain but on the living brain made possible by the widespread use of MRI. It is almost impossible to pick up a current psychiatric journal and not see a study of anatomical measurements made on MRI scans comparing patients with a psychiatric diagnosis with healthy subjects. And it is also almost impossible for the study not to report differences in these measurements between comparison groups. Indeed, patients with anxiety disorders are said to have changes in amygdala volume, while patients with depression have smaller hippocampi and thinner cingulate cortices. Schizophrenia shows widespread reductions in cortical measurements, which often are found to get worse over time.

While these reported differences have been the subject of some controversy and debate (1–3), it has become research lore that structural changes in the brain are characteristic of many psychiatric disorders and are likely clues to primary neurobiology (4). Even some variations in normal behavior (e.g., watching pornographic Internet videos [5]) are claimed to be associated with structural changes in the brain. These various findings are routinely referred to as “cortical thinning,” “atrophy,” “tissue loss,” or worse, and they are assumed to be

insights into the underlying nature of these conditions. We write to offer a note of caution about this renaissance in studies of psychiatric patients based on MRI data because we believe the evidence that these “findings” are reflections of changes in the brain related to pathogenesis is inconclusive at best and potentially represents artifacts or epiphenomena of dubious value. Moreover, by perpetuating from study to study the uncritical instantiation of findings potentially representing fallacies of all sorts, there is a serious risk of misinforming our colleagues and our patients about biological abnormalities associated with psychiatric illness. Before offering our comments (with full acknowledgment that we ourselves have contributed in the past to the very literature that we are now raising questions about), we first advise the reader about the scope of this commentary:

1. One primary goal is to challenge the jargon and, ultimately, the meaning associated with MRI-based differences between patients and controls (e.g., “cortical loss,” “gray-matter volume reductions,” “tissue loss,” “abnormal connectivity,” “default mode deficit,” etc.). We do not question the veracity of the large number of studies reporting these findings.
2. We highlight a sizable list of diverse confounders of MRI data, not as the “true” explanation for the findings but rather as a counterbalance to the same jargon and as a rationale for questioning the meaning of the findings.
3. While we rely on technical reports to substantiate our commentary, this is not a technical review. It is an opening chapter in a critical perspective on the interpretation of MRI results in psychiatric research.

See related feature: **AJP Audio** (online)

4. The overarching purpose of this cautionary note is to encourage a discussion about a widely and tacitly recognized, though mostly ignored, "inconvenient" truth: that conventional MRI does not allow us to make firm inferences about the primary biology of mental disorders and that we need to acknowledge this as a starting point in realizing the full value of MRI studies in psychiatry.

In launching this debate, we first recapitulate the nature of popular MRI measurements, then highlight documented systematic confounders, and then offer a more cautious perspective for interpreting MRI results in psychiatry.

Structural MRI is not a Direct Measure of Brain Structure

When evaluating claims of anatomical differences in comparison samples based on MRI measurements, it is important to recall what MRI actually is. MRI is not a direct measure of brain structure. MRI is a physical-chemical measure, based on radio-frequency signals emitted from energized hydrogen atoms influenced by the magnetic properties of the microenvironment of surrounding tissue. Contrasts between tissue compartments (i.e., gray and white matter, vasculature, and CSF), which are critical parameters in making anatomical measurements, depend on the relative signals coming from these components. The source of MRI contrast between soft tissues is related to the density of protons (H^+) and their magnetic properties (expressed by the so-called T_1 and T_2 relaxation constants). While proton density is relatively homogeneous for most tissues, T_1 and T_2 can vary dramatically from one tissue to another (e.g., gray and white matter, and CSF), are strongly influenced by viscosity and rigidity, and can be manipulated by varying one parameter or another used to collect MR signals (through the so-called weightings of MRI pulse sequence protocols [6]). Of note, from a biochemical perspective, the principal and direct contributors to the MR signal are protons in free water, fat, and "bound" water. Conversely, the "macromolecules" (i.e., membrane phospholipids, myelin's sphingolipids, proteins) do not directly and efficiently contribute to the MR signal; rather, they modulate the signal from water protons. In other words, MR signals are based on highly rarefied parameters and metrics that are susceptible to many physical-chemical phenomena not necessarily related to the number or architecture of the cells in the tissue.

Consider, for instance, "gray matter volume," the main readout of voxel-based morphometry analyses, a popular automated algorithm for making anatomical measurements. In the original description of this method, Ashburner and Friston (7) explain that volume is derived from a complicated segmentation algorithm applied to the intensity (i.e., the "brightness") of the voxel-based morphometry unit (voxel) on the T_1 -weighted images that allows for separation of gray matter from white matter and CSF spaces. The dimension of the typical voxel (i.e., the resolution) of the standard human structural MRI is in excess of 1 mm^3 . At the microscopic level, a gray matter voxel of this size is actually a heterogeneous tissue sample comprising

neurons, neuropil, glia, microvessels, and extracellular space. Any of these components is susceptible to alterations triggered by a multitude of biophysical factors that may contribute to a change in voxel intensity on MRI having nothing to do with the structural integrity of the tissue.

Indeed, variation in MRI signals and anatomical measurements have been reported for a vast array of nonstructural factors, including common psychotropic drug use (8–10), changes in body weight (11–13), blood lipid levels, alcohol use, nicotine use, cannabis use, exercise, hydration, pain, and cortisol levels (14–18), to name just a few. While it is unclear how each of these factors specifically affects the MRI signal, it is likely that they alter the biochemistry and thus the magnetic properties of the tissue rather than the number or basic structure of cells. Thus, before jumping to the conclusion that MRI differences between a patient sample and a control sample represent microstructural abnormalities of pathogenic significance, one needs to be mindful of other plausible possibilities. For example, a simple change in brain perfusion associated with acute drug administration has been shown to masquerade as a change in MRI volume measurements (19). In this context, it is worth remembering that a major component of the volume of a living brain is perfused vasculature. Drugs also can change the magnetic properties that determine the T_1 relaxation time, a critical measure in determining the signal contrast between gray and white matter, on which gray matter morphometry is based (9).

It might be argued that in studies of healthy individuals, these nonstructural factors are "white noise" elements that do not systematically vary from one individual to another and thus are not likely to confound the measurements in a systematic way. In other words, in comparisons of healthy subjects grouped by a factor that does not vary systematically with any of the confounders above, these concerns may not be relevant. This may be a relative strength, for example, of so-called imaging genetic MRI studies (20), where demographically matched healthy subjects are compared based on genetic variation. While the confounders mentioned above may represent noise in the sample and reduce the power of genetic association, they are much less likely to vary systematically from one genotype to another and spuriously account for an association. However, we caution here, too, that even in such seemingly unconfounded studies, occult confounding may still exist. For example, differences in temperament (e.g., stress sensitivity) or in smoking behavior, both of which may influence MRI signals, may differ by genotype group and masquerade as apparent genetic associations with MRI phenotypes.

Systematic Confounding in Case-Control Studies

Unfortunately, in studies of psychiatric patients, or even in studies of subjects across age or other demographic characteristics, these various confounding factors typically vary quite systematically between samples and bias results based on their effects. For example, patient samples often differ from controls in smoking history, alcohol or cannabis use, exercise, body

weight, lipid levels, ongoing stress (and therefore elevated endogenous corticosteroid levels), and medication use. A particularly troubling confounder that is also likely to vary systematically across contrasting samples is head motion during a scan. A recent report demonstrated that even subtle motion, and even after removing obvious motion artifacts and controlling for motion with the standard algorithms used in state-of-the-art MRI studies, still leads to spurious findings of cortical volume and thickness reductions (21). Moreover, the reductions show a regional distribution favoring medial and lateral cortical regions, quite typical of that described in many reports of psychiatric patients. Is it so far-fetched to imagine that some patients have a harder time remaining motionless during the 10–20 minutes of the typical scan procedure compared with control subjects, many of whom are paid volunteers who often have considerable prior exposure to the constrained and noisy MRI environment?

Although this would seem a legitimate question, a wealth of findings are typically interpreted as “structural” changes while the corrupting potential of various artifacts, including occult movement, is trivialized or dismissed. For example, a recent comprehensive review of MRI findings in people at increased risk of psychosis (clinical and genetic) and of early-onset schizophrenia listed more than 110 structural MRI studies published between 1996 and 2013 (22). Although the tabulated results suggest a substantial degree of inconsistency and lack of replication across various studies with differences virtually all over the brain, and although areas susceptible to motion artifacts, partial volume, or drug effects are over-represented in the findings (i.e., midline and lateral cortical structures, insula, and medial temporal lobe), the interpretation stressed an “accelerated fronto-temporal cortical [gray matter] volume reduction across the spectrum of schizophrenia risk” (22). While the authors acknowledge the variability and limited replicability of the studies, they attribute this to “clinical heterogeneity” and “diversity of neuroimaging methods used for acquisition and analysis of MRI data” (22). While these may be important factors, we suggest that the systematic confounders noted above cannot be dismissed as a less likely explanation.

Even reviews specifically addressing the confounders associated with MRI findings in schizophrenia (e.g., antipsychotic medication, cannabis, and smoking) start from an axiomatic assertion of “substantial evidence for excessive tissue loss” in schizophrenia, grossly based on MRI data (23). The tendency of MRI researchers to attribute pathobiological meaning to their findings is understandable, and we ourselves have yielded to this temptation.

Indeed, some of our own findings that seemed at the time to provide potentially important insight about the fundamental neurobiology of schizophrenia appear to us problematic in the current context. For example, in a high-profile study of discordant monozygotic twins, Suddath et al. (24) reported that affected twins had smaller hippocampal volume than did their healthy unaffected co-twins. Of note, the finding of hippocampal volume reduction became virtual dogma in studies of patients with schizophrenia, although

evidence of gross hippocampal pathology is not a consistent finding in postmortem brain of patients with schizophrenia and also is not typically found in healthy siblings of patients with schizophrenia (25, 26). In view of our current understanding of factors influencing variability of hippocampal volume measured with MRI, how can we now have confidence that this putatively landmark finding was not a reflection of greater stress and endogenous corticosteroid levels, or of limited physical activity, or differences in body weight, or of a drug effect in the affected twin? To reiterate: we do not dismiss the possibility of hippocampal structural abnormalities in schizophrenia or other structural alterations for that matter, and we recognize that many of the chemical and physiological confounders mentioned above may induce neuroplastic changes in neuronal microstructure and dendritic architecture (e.g., corticosteroid elevations). However, these are structural epiphenomena, not primary pathobiology and not specific to psychiatric patients. We caution that the potential confounding does not allow for the default interpretation to be that such changes are primary neuropathological components of schizophrenia or other psychiatric disorders per se. It is worth noting that the putatively “substantial evidence for excessive tissue loss” in schizophrenia observed with MRI should be obvious on classical neuropathological examination, but more than 100 years of postmortem studies since Alzheimer performed the first neuropathological study of a schizophrenia patient have failed to confirm it.

These considerations and concerns apply to other anatomical techniques, such as diffusion tensor imaging (DTI), which has been reported to reveal abnormal white matter structure in most psychiatric patient studies. DTI is an even more highly derived measure than MRI morphometry, and it is subject to most of the same confounders. As stressed in recent reviews (27, 28), caution in data interpretation is essential, especially in clinical populations, because DTI is influenced by many nonanatomical factors and involves complex processing and analysis that most studies fail to address. Indeed, according to recent technical reviews (27, 29), numerous defined pitfalls characterize a number of DTI studies. These pitfalls are related to the particular difficulties in image acquisition and susceptibility to artifacts caused by motion and magnetic field inhomogeneities and a complex analytic space prone to produce erroneous results. Again, we do not maintain that white matter abnormalities are not associated with psychiatric disorders, only that the potential systematic confounders of DTI studies in psychiatric patients make this conclusion seem no more likely than the alternative.

Systematic Confounding in Functional MRI Studies

Our concerns about structural anatomy do not spare the equally frequent reports in our literature of functional anatomical differences observed in contrasting ill and well samples using functional MRI (fMRI) approaches. It is worth restating here that fMRI, with its noninvasive potential for indirectly measuring brain activity in association with task-induced mental

processes, rapidly became the preferred technique for in vivo functional brain studies, both with scientists and the lay public. Consequently, during the more than 20 years since its public unveiling in 1992 (30), fMRI has incited passionate discussion and debate, especially regarding the promise of deciphering the neural substrate of human normal and pathological behavior and the potential confounders of fMRI data and pitfalls in statistical analysis (31, 32). We invite interested readers to consult ample reviews about what fMRI can and cannot do, and about controlling the potential confounders in acquiring and analyzing the main readout of fMRI, the blood-oxygen-level-dependent (BOLD) response (31, 33, 34). Dramatic improvements in fMRI design and analysis have occurred over the years by implementing sophisticated tools for minimizing and correcting artifacts and the development of routine guidelines for reporting and interpreting fMRI results (35). Our note of caution here applies to particular applications of fMRI in studies comparing clinical populations with mental disorders and control subjects.

Echoing the concerns about structural MRI, we propose that confounders biased toward patient samples, particularly motion and mental state, are a serious concern in fMRI reports as well. We suggest caution in assuming that any fMRI approach can conclusively remove these concerns, but in principle, so-called activation paradigms, where subjects are their own control and one cognitive state is compared with another, and where rigorous correction methods for artifacts can be applied across the alternating states, offer some implicit reassurance and control. This conclusion is based on the assumption that the confounders noted above should not selectively bias the BOLD response during one phase of an activation protocol and not another and that confounders should represent nonsystematic noise controlled by the within-subject activation design. Even so, one cannot be certain that motion effects, or drug effects, or anxiety, etc. would not disproportionately influence one state and not another, particularly if one state is more anxiety producing or more likely to induce motion than another. In principle, fMRI data analysis routines are able to identify such biased confounding and control for it or remove epochs in the time series that are so affected, but these correction strategies also may impose a cost (see below). In sum, artifacts inherent in such confounding would seem less problematic in within-subject activation designs than in comparisons across subjects where there is no within-subject reference and where correction procedures are thus inherently more difficult to implement (see below).

It is also important to note that while activation-based fMRI studies are relatively protected from the confounding issues noted above, the meaning of differences observed between patients and controls is still not easily interpreted, and considerable controversy exists about the relationship of the BOLD signal to underlying neural activity. Our emphasis here is again only about interpretation of differences between patient and control groups and the potential role of systematic confounders. While it is popular to interpret such differences between groups as related to illness pathophysiology, they may instead reflect

epiphenomena related primarily to the state of illness. For example, drugs, alcohol, cannabis use, and ongoing symptoms may influence cortical activation patterns just as they influence performance on cognitive tests. Patients may perceive the stimuli differently, have difficulty remaining "on task" for the duration of the protocol, or be distracted by ongoing symptoms or extraneous stimuli. One approach that has been advocated to identify fMRI activation patterns of brain function associated with risk for illness but not confounded by the state of illness is to study healthy siblings of patients (36).

The Conundrum of Resting-State fMRI

The fMRI studies of functional anatomy that we do believe raise especially serious concerns analogous to the structural studies are those that do not employ a within-subject reference state. These are the so-called resting-state fMRI studies. To the extent that functional neuroimaging data reflect what the brain is doing during the imaging protocol, the challenge for the investigator is to figure out what the brain was actually doing. With cognitive activation paradigms, there is at least a gross readout of what the subject is doing during the scan; that is, the performance on the task. With resting-state fMRI, this is a much murkier problem because subjects lie in the confining and noisy environment of the MRI scanner for typically up to 10 minutes doing nothing. This is said to be a resting or unstimulated state, and the pattern of activity typically seen in healthy subjects correlated across multiple brain regions is called the "default mode network." This pattern was originally interpreted as a fundamental signature of brain connectivity and was rapidly invested with major functional relevance (for a review, see reference 37), even though cautions soon emerged about the potential role of a multitude of cognitive, behavioral, and physiological variables, as well as artifacts and conceptual inconsistencies (38–41).

Part of the appeal of the resting-state fMRI paradigm is that it is easy to do and easy to find differences between patient and control samples. Again, there is almost no study in the literature that has not shown differences between ill and healthy groups. Patients with a variety of psychiatric diagnoses have been observed to have deviations from the default pattern, and it is often stated that they show a deficiency or abnormality of the default network as if this is some sort of neural defect. In fact, it is unimaginable that patients with schizophrenia or depression or autism will experience the MRI environment analogously to a paid healthy volunteer, and it is unlikely that they will each experience it the same. The different ways in which they are liable to think and feel about the noise and the confinement will interfere with the so-called default pattern or with engagement of other so-called network profiles, producing a degree of "abnormality." Indeed, an analogous "abnormality" has been demonstrated in healthy subjects who are instructed to vary what they attend to during the resting state (42). It is also important to highlight a recent study by Smith et al. (43) using high temporal resolution fMRI during the resting state that found that individuals tend to experience the "resting" MRI

environment quite individually, with varying degrees of vacillation between diverse and transient mental states and neural systems, the summation of which is the reductionist “default network” signal. The degree to which individuals vary in their shifting experience determines their individual set of transient “brain states” and ultimately their expression of many so-called brain networks in addition to the derived default mode network. How can we have confidence that differences found between patient samples and control individuals do not simply reflect the fact that the patients do not “zone out” as routinely as the controls during the acquisition of data?

In addition to the likelihood that resting-state brain activity variation reflects the subjective experience of being scanned by MRI, we would highlight again the corrupting influence of head movement and other motion artifacts (44) on resting-state fMRI, as it is again a particularly worrisome confounder that usual correction methods fail to control (40, 45). Of note, the midline structures of the default mode network seem to suffer considerably from spurious but systematic correlations generated by even minor head motion, particularly nodding motions. In a sober conclusion from the study of Power et al. (45), the authors suggest that resting-state fMRI studies in clinical populations need a major reanalysis and a reinterpretation of results. A recent exhaustive account of the state of the art in motion correction in resting-state fMRI suggests that in spite of progress in identifying this potential artifact, this issue is not resolved, and ongoing work to minimize the undesirable effect is still under construction (40).

We would prefer to conclude this section with some suggestions for avoiding the potential pitfalls of resting-state MRI studies comparing patient and control samples. Several recent reports have offered guidelines to reduce artifacts and to provide objective data about their contribution to a given study (40, 44). However, none of these approaches removes the problems we have enumerated. For example, one now widely used method for motion correction in resting-state fMRI studies involves censoring out the segments of an fMRI time series in which movement has occurred (so-called scrubbing of the data) often with interpolation to temporally “fill in” the missing data points with synthetic data; however, the number of such segments that must be removed and thus accounted for is likely to be larger in patient samples, and even if an equivalent number of segments are removed from the control group to match the content of the data sets, differences in the temporal clustering of these segments and ensuing differences in the distribution of the temporal correlations across the data are likely to be introduced (40, 45). A relatively new fMRI method, multiecho acquisition, has been suggested as a way to reduce movement artifacts (46, 47), but there has been little work on the efficacy of this approach in clinical cohorts. Furthermore, none of these approaches to resting-state fMRI artifacts addresses the issue of the personal experience during the scan.

It has become increasingly popular in recent years to try to validate imaging findings by acquiring multimodal MRI and independent biological data and applying multivariate analytical techniques, along with as good as possible quality-control

measures (48, 49). We maintain, however, that pushing interpretation of results toward the pathobiological pole is still premature regardless of the high dimensionality of the data and the sophistication of the statistics, because multivariate statistics do not remove drug, smoking, or corticosteroid effects or account for mental state variation, and many of the confounders are actually *trans*-modal. In other words, they can potentially affect the same regions across imaging modalities or diverse biological measures other than imaging. For example, the anterior cingulate cortex and other midline structures could be affected by movement in structural MRI, DTI, and resting-state fMRI, and stress, drug use, or tobacco use can affect both peripheral measures and MRI epiphenomena and account for their correlation.

In searching for a way out of this conundrum, one might suggest that if sample sizes become very large, the various artifacts would cancel out, analogous to heterogeneity issues in large population-based genetic studies. We doubt this would work because as heterogeneous as the artifacts may be from one individual to another (i.e., some subjects move, others are taking drugs or consumed alcohol or cannabis the night before the scan, others smoke, others are anxious or delusional, etc.), all these diverse effects converge on the same MRI readout in the form of reduced structural measures or altered resting-state fMRI patterns in the patient sample.

A Cautious Perspective for Future MRI Research in Psychiatry

While we cannot offer a formula for deconvoluting the concerns we have enumerated from the existing results of MRI studies in psychiatric patients, we propose instead a change of perspective in future MRI research when patient and control samples are directly compared. We recommend that researchers using structural MRI techniques remain highly skeptical of the basis of changes that are found in comparisons of patient and control samples and refer to them as “differences in MRI measurements,” not as “cortical thinning” or “loss.” Patient samples should be carefully characterized for potential confounders, especially those that tend to be systematically different from controls and that influence MRI measures, such as smoking, alcohol and cannabis use, body weight, blood lipid levels, corticosteroid levels, exercise routines, and general health. These characteristics should be included in a description of the samples. Head motion parameters, breathing patterns, and skin conductance measures also should be recorded and included as part of the data of a study. Resting-state fMRI studies of patient samples should be interpreted with forthright acknowledgment of the uncertainty of what the patterns of activity reflect, particularly with respect to an “abnormality.” If data are “scrubbed” to remove artifacts, the degree to which the time series data are altered should be described in detail. Given the preeminent role of mental experience during the resting-state scan, interpreting the patterns in patients as a “defect” is not justified.

We argue that fMRI studies of patient samples should preferably be task-induced, where every subject is his or her

own control and artifacts can be surveyed across the time series of data and contrasted from one state to another. In designing fMRI activation paradigms for psychiatric subjects, it will be important to account for patients' cognitive capabilities and emotional characteristics, a caution formulated some time ago (50) but seldom implemented. Even with careful implementation of these caveats, fMRI studies during activation paradigms may uncover state effects (e.g., medication, stress, symptoms) and not underlying illness pathophysiology. We encourage investigators seeking to confirm that findings in patient samples are not such epiphenomena to study carefully screened and healthy siblings and, further, to engage in repeated studies of the same subjects to identify effects that are at least enduring and not coincidental. Indeed, a number of "structural changes" related to the confounders that we highlight are reversible (51–53). We also suggest that more consideration be given to adding arterial spin tagging protocols to imaging studies to elucidate the potential role of changes in perfusion as a "cause" of apparent structural and functional variation. Of note, methodological advancements in perfusion techniques, which provide absolute quantification of regional blood flow, are making these approaches more relevant for clinical research in psychiatry (54, 55). Again, even with the application of comprehensive, systematic, and complementary multimodal MRI, it will not be easy to disentangle cause from effect. This will require the development of innovative approaches that challenge the brain with controlled experimental interventions and that induce or rescue the observed variations.

We have reached a crossroads in neuroimaging studies in psychiatry research. To advance on the path of understanding the pathobiology of mental disorders with these methods, we advocate keeping these caveats prominently in mind in the design of future studies, while researchers critically approach the interpretation of results. We expect that continuing technological advances based on a more "biological" understanding of the MRI signal will allow a fuller characterization of factors that link MRI signals to brain anatomy and function (56). In the meantime, we opine that current studies are plagued by so many possible systematic confounders that one can only wonder whether, like Wolfgang Pauli, "these results are not only not right, they are not even wrong!" We would caution that researchers and clinicians pause and rethink carefully the conclusions that can be drawn from these various MRI findings in psychiatric research. We hope that the few recommendations we have sketched above encourage a necessary discussion about the future of MRI studies in psychiatry.

AUTHOR AND ARTICLE INFORMATION

From the Lieber Institute for Brain Development, Johns Hopkins University, Baltimore; and the Departments of Psychiatry and Behavioral Sciences, Neurology and Neurosurgery, and Neuroscience, and the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore.

Address correspondence to Dr. Weinberger (drweinberger@libd.org).

The authors thank their colleagues for helpful comments on the manuscript and are particularly grateful for the substantive suggestions of Danny Chen, Venkata Mattay, and Karen Berman.

The authors report no financial relationships with commercial interests.

Received June 11, 2015; revision received June 23, 2015; accepted June 29, 2015; published online Aug. 28, 2015.

REFERENCES

- Weinberger DR, McClure RK: Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry* 2002; 59:553–558
- Zipursky RB, Reilly TJ, Murray RM: The myth of schizophrenia as a progressive brain disease. *Schizophr Bull* 2013; 39:1363–1372
- Savitz JB, Rauch SL, Drevets WC: Clinical application of brain imaging for the diagnosis of mood disorders: the current state of play. *Mol Psychiatry* 2013; 18:528–539
- Kahn RS, Sommer IE: The neurobiology and treatment of first-episode schizophrenia. *Mol Psychiatry* 2015; 20:84–97
- Kühn S, Gallinat J: Brain structure and functional connectivity associated with pornography consumption: the brain on porn. *JAMA Psychiatry* 2014; 71:827–834
- Johnson KA, Becker JA: The Whole Brain Atlas. <http://www.med.harvard.edu/aanlib>
- Ashburner J, Friston KJ: Voxel-based morphometry: the methods. *Neuroimage* 2000; 11:805–821
- Lesh TA, Tanase C, Geib BR, et al: A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry* 2015; 72:226–234
- Cousins DA, Aribisala B, Nicol Ferrier I, et al: Lithium, gray matter, and magnetic resonance imaging signal. *Biol Psychiatry* 2013; 73:652–657
- Arnone D, McKie S, Elliott R, et al: State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry* 2013; 18:1265–1272
- Walther K, Birdsill AC, Glisky EL, et al: Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp* 2010; 31:1052–1064
- Amianto F, Caroppo P, D'Agata F, et al: Brain volumetric abnormalities in patients with anorexia and bulimia nervosa: a voxel-based morphometry study. *Psychiatry Res* 2013; 213:210–216
- Friederich HC, Walther S, Bendszus M, et al: Grey matter abnormalities within cortico-limbic-striatal circuits in acute and weight-restored anorexia nervosa patients. *Neuroimage* 2012; 59:1106–1113
- Fritz HC, Wittfeld K, Schmidt CO, et al: Current smoking and reduced gray matter volume: a voxel-based morphometry study. *Neuropsychopharmacology* 2014; 39:2594–2600
- Streitbürger DP, Möller HE, Tittgemeyer M, et al: Investigating structural brain changes of dehydration using voxel-based morphometry. *PLoS One* 2012; 7:e44195
- Erickson KI, Voss MW, Prakash RS, et al: Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA* 2011; 108:3017–3022
- Ward MA, Bendlin BB, McLaren DG, et al: Low HDL cholesterol is associated with lower gray matter volume in cognitively healthy adults. *Front Aging Neurosci* 2010; 2:29
- Filbey FM, Aslan S, Calhoun VD, et al: Long-term effects of marijuana use on the brain. *Proc Natl Acad Sci USA* 2014; 111:16913–16918
- Franklin TR, Wang Z, Shin J, et al: A VBM study demonstrating 'apparent' effects of a single dose of medication on T1-weighted MRIs. *Brain Struct Funct* 2013; 218:97–104
- Hariri AR, Weinberger DR: Imaging genomics. *Br Med Bull* 2003; 65:259–270
- Reuter M, Tisdall MD, Qureshi A, et al: Head motion during MRI acquisition reduces gray matter volume and thickness estimates. *Neuroimage* 2015; 107:107–115

22. Brent BK, Thermenos HW, Keshavan MS, et al: Gray matter alterations in schizophrenia high-risk youth and early-onset schizophrenia: a review of structural MRI findings. *Child Adolesc Psychiatr Clin N Am* 2013; 22:689–714
23. Van Haren NE, Cahn W, Hulshoff Pol HE, et al: Confounders of excessive brain volume loss in schizophrenia. *Neurosci Biobehav Rev* 2013; 37:2418–2423
24. Suddath RL, Christison GW, Torrey EF, et al: Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med* 1990; 322:789–794
25. Goldman AL, Pezawas L, Mattay VS, et al: Heritability of brain morphology related to schizophrenia: a large-scale automated magnetic resonance imaging segmentation study. *Biol Psychiatry* 2008; 63:475–483
26. Honea R, Crow TJ, Passingham D, et al: Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry* 2005; 162:2233–2245
27. Jones DK, Knösche TR, Turner R: White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 2013; 73:239–254
28. Marengo S, Radulescu E: Imaging genetics of structural brain connectivity and neural integrity markers. *Neuroimage* 2010; 53:848–856
29. Jones DK, Cercignani M: Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed* 2010; 23:803–820
30. Kim SG, Ogawa S: Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. *J Cereb Blood Flow Metab* 2012; 32:1188–1206
31. Haller S, Bartsch AJ: Pitfalls in FMRI. *Eur Radiol* 2009; 19: 2689–2706
32. Vul E, Pashler H: Voodoo and circularity errors. *Neuroimage* 2012; 62:945–948
33. Uğurbil K, Toth L, Kim DS: How accurate is magnetic resonance imaging of brain function? *Trends Neurosci* 2003; 26:108–114
34. Logothetis NK: What we can do and what we cannot do with fMRI. *Nature* 2008; 453:869–878
35. Poldrack RA, Fletcher PC, Henson RN, et al: Guidelines for reporting an fMRI study. *Neuroimage* 2008; 40:409–414
36. Rasetti R, Weinberger DR: Intermediate phenotypes in psychiatric disorders. *Curr Opin Genet Dev* 2011; 21:340–348
37. Buckner RL, Andrews-Hanna JR, Schacter DL: The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008; 1124:1–38
38. Morcom AM, Fletcher PC: Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage* 2007; 37:1073–1082
39. Buckner RL, Krienen FM, Yeo BT: Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci* 2013; 16:832–837
40. Power JD, Schlaggar BL, Petersen SE: Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage* 2015; 105:536–551
41. Murphy K, Birn RM, Bandettini PA: Resting-state fMRI confounds and cleanup. *Neuroimage* 2013; 80:349–359
42. Benjamin C, Lieberman DA, Chang M, et al: The influence of rest period instructions on the default mode network. *Front Hum Neurosci* 2010; 4:218
43. Smith SM, Miller KL, Moeller S, et al: Temporally-independent functional modes of spontaneous brain activity. *Proc Natl Acad Sci USA* 2012; 109:3131–3136
44. Birn RM, Diamond JB, Smith MA, et al: Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage* 2006; 31:1536–1548
45. Power JD, Barnes KA, Snyder AZ, et al: Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012; 59:2142–2154
46. Kundu P, Inati SJ, Evans JW, et al: Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI. *Neuroimage* 2012; 60:1759–1770
47. Kundu P, Brenowitz ND, Voon V, et al: Integrated strategy for improving functional connectivity mapping using multiecho fMRI. *Proc Natl Acad Sci USA* 2013; 110:16187–16192
48. Cannon TD, Chung Y, He G, et al: Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry* 2015; 77:147–157
49. Goodkind M, Eickhoff SB, Oathes DJ, et al: Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* 2015; 72:305–315
50. Price CJ, Friston KJ: Scanning patients with tasks they can perform. *Hum Brain Mapp* 1999; 8:102–108
51. Karama S, Ducharme S, Corley J, et al: Cigarette smoking and thinning of the brain's cortex. *Mol Psychiatry* 2015; 20:778–785
52. Kühn S, Charlet K, Schubert F, et al: Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. *JAMA Psychiatry* 2014; 71: 806–811
53. Rodriguez-Raecke R, Niemeier A, Ihle K, et al: Structural brain changes in chronic pain reflect probably neither damage nor atrophy. *PLoS One* 2013; 8:e54475
54. Gai ND, Talagala SL, Butman JA: Whole-brain cerebral blood flow mapping using 3D echo planar imaging and pulsed arterial tagging. *J Magn Reson Imaging* 2011; 33:287–295
55. Jahanian H, Peltier S, Noll DC, et al: Arterial cerebral blood volume-weighted functional MRI using pseudocontinuous arterial spin tagging (AVAST). *Magn Reson Med* 2015; 73:1053–1064
56. Dinse J, Härtwich N, Waehnert MD, et al: A cytoarchitecture-driven myelin model reveals area-specific signatures in human primary and secondary areas using ultra-high resolution in-vivo brain MRI. *Neuroimage* 2015; 114:71–87