MRI artifacts in psychiatry: Head motion, breathing, and other systematic confounds

9

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To better understand psychiatric conditions, we rarely look at the brains of cadavers any more, but that was common practice some hundred years ago. Today, magnetic resonance imaging (MRI) and functional MRI (fMRI), to give one example, permit structural and functional investigation of the biology of psychiatric conditions in the living human brain. And yet, many subtle pitfalls linger when imaging the neural infrastructure, let alone neural activity, in search of higher brain functions.

Not only does the popular science press burst at the seams with images of scanned brains, leading psychiatry journals now regularly include findings from brain imaging assays. A typical experiment may draw on about two dozen people from one group, often individuals diagnosed with a mental disorder, and compare these patients to a comparably sized group of controls. Unfortunately, these findings tell us considerably less than most readers appreciate. Why? Mostly because of inadequate statistical power (see Chapter 12) and systematic confounds. For example, patients and controls often differ with respect to traits that alter brain data (e.g., head motion in the scanner) without necessarily affecting the underlying neural activity. Such confounds pervade findings from both structural and functional brain imaging research.

With structural brain imaging, we often hear largely accepted, but nonetheless questionable, statements such as "anxiety alters amygdala volume," "depression shrinks hippocampus and cingulate cortex," and "schizophrenia eats away at cortical matter." While debate wages on, many researchers acquiesce to the notion that structural brain changes are a primary characteristic of psychiatric disorders [1]. Some researchers even claim that nonpathological behaviors, such as watching porn [2], alter the structure of our brain. Thus we apply diagnostic terms, such as "cortical thinning," "atrophy," "tissue loss," and "abnormal connectivity," and we assume that these are insights into the underlying nature of these conditions [3].

We'd like to make sure you fully understand our point: we don't challenge the findings that these studies report; instead, we contest the jargon filled, authoritative mode, which colors their seemingly conclusive claims. Such presentations conceal

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a largely ignored, inconvenient truth: MRI scarcely allows us to make firm inferences about the neurobiology of mental disorders.

To begin to understand why, remind yourself what this imaging technique really measures. MRI does not directly assess brain structure (see Chapter 8). Rather, it measures the properties of hydrogen atoms and depends on the magnetic properties of the microenvironment surrounding the tissue. In other words, MR signals are susceptible to many physical−chemical phenomena possibly unrelated to the number (or structure) of cells in tissue.

When MRI scans emerge as evidence for a linkage between a given psychiatric condition and a certain pathology of brain structures, we must consider alternative, nonanatomical explanations. For example, some factors that influence MR signals include history of smoking, alcohol, cannabis/psychedelic drugs, exercise, body weight, lipid levels, ongoing stress, and medication.

Slight head motion during a scan can wield a substantial impact on MRI findings. So "professional" control participants—that is, individuals who partake in multiple MRI experiments as paid volunteers—would likely have the advantage of keeping more still, compared to the uninitiated. Now imagine individuals diagnosed with a psychiatric disorder, their symptoms managed by medication, entering an MRI machine for the first time and asked to lie motionless for extended periods of time. Is it possible the image from the patient brain exhibits "cortical volume and thickness reduction," or was the difference a function of how the patient subtely *moved* compared to a control participant?

To further illustrate this point, consider the "excessive tissue loss" in the hippocampus observed via MRI in schizophrenic patients. If this observation were a result of abnormalities in the neurobiology, then evidence of such tissue loss should be apparent upon a postmortem examination. Alas, more than a hundred years of postmortem studies have scantily confirmed this MRI-based result [3].

In fMRI experiments, we usually see "activation" studies, where participants perform a particular task, and "resting-state" studies where participants lie passively in the scanner without any specific cognitive goal. Over a thousand peer-review scientific reports on fMRI are published each year, and yet most of these articles neglect to mention common confounds—often the very same ones that plague structural MRI findings. While fMRI has improved dramatically since its inception in 1992, researchers still fall into the same traps of oversight and omission when comparing patients to healthy controls.

Within activation studies, rigorous experimental designs can offset many a confound. However, resting-state fMRI studies, where participants go through a scan without a specific task, pose a conundrum because participants experience the scanning process very differently, thereby exerting a dramatic impact on fMRI data. To demonstrate why many resting-state fMRI findings are likely spurious, one research group looked at a dataset of 500 brain scans, all taken from healthy controls, and tested every permutation of 20 brains compared to 20 other brains [4]. They found

significant differences between the two groups of brains in up to 70% of cases. Moreover, they used the default setting in many statistical packages, which assumes that fMRI data follow a certain distribution, although that's frequently untrue. In other words, some "standard methods" of analysis that rest on unreliable assumption can easily produce false positives. Thus we must remain wary of the default statistical methods as we attempt to sort out results: from the robust to the flimsy.

Rather than direct neural activity, fMRI measures the content of oxygen in the blood circulating throughout the brain (the blood oxygen level dependent (BOLD) signal). If we hold our breath during a scan, we can drive a 3%−6% change in the BOLD signal [5−7]. Meanwhile, most fMRI studies find differences of less than 1% between experimental groups. Moreover, not just holding the breath, but subtle variations in respiratory rate and depth—patterns that occur naturally over time—can also markedly sway the BOLD signal [8,9]. Can you imagine breathing differences when you cram anxious patients into an MRI scanner and compare them to healthy controls? Is it possible that these two groups would breathe differently? Don't hold your breath for the correct answer.

Two "hot" regions in brain imaging research—the anterior cingulate and the insula—are particularly susceptible to respiratory artifacts. Could their fame rely on such inhale−exhale confounds? Perhaps, but we would need further studies to confirm. With appropriate methodology, including a chest belt and some statistical modeling, we can control for and rule out a substantial portion of this potential artifact. And yet, not all neuroimagers pursue this direction.

Now consider imaging the brains of expert meditators, say Buddhist monks who have been practicing their contemplative tradition for decades. If we compared their resting state to that of naïve controls, would you not expect the monks to be thinking about very different things? Would you not suppose that they breathe differently? Lining up a large sample of expert meditators would make for a tall order, so a small group would have to do and the possibility of a false positive would accordingly become more prominent, especially if we draw on default statistical tests. To properly evaluate fMRI resting-state findings, we would need to account, at the very least, for the sample size and what participants were pondering, whether the researchers had regressed out distortion from breathing, and whether they used appropriate stats.

The status of neuroimaging research in psychiatry seems tenuous. On the one hand, (f)MRI remains an important tool for understanding the psychopathology and pathobiology of mental disorders. On the other hand, to make further advances, researchers ought to keep in mind the caveats we have highlighted herein, and

which remain heretofore largely unaddressed. Toward this end, clinicians and researchers stand to benefit from designing and interpreting experiments that account for such potential artifacts. We would do well to critically rethink the inferences we sometimes draw from (f)MRI studies of mental health.

Additional readings

The experiment showing a high rate of false-positive in certain types of fMRI studies: Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci USA 2016;113(7900−7905):201602413. Available from: https://doi.org/10.1073/pnas.1602413113.

A more in depth discussion on artifacts in (f)MRI, and inspiration for this chapter: Weinberger DR, Radulescu E. Finding the elusive psychiatric "lesion" with 21st-century neuroanatomy: a note of caution. Am J Psychiatry 2016;173(1):27−33. Available from: https://doi.org/10.1176/appi.ajp.2015.15060753.