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Mental disorders in entangled brains

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ABSTRACT

In this commentary on Anneli Jefferson's book "Are Mental Disorders Brain Disorders?," I offer an overview of her central thesis, and then propose my own modified account of when we are justified in calling mental disorders as "brain disorders." In doing so, I draw on recent work in neuroscience that understands the relationship between brain and behavior in complex, dynamic, and computational terms. In particular, I disagree with Jefferson's criterion of sufficiency, that a particular brain process should always realize a psychological dysfunction. I propose that a psychiatric disorder can be said to be a brain disorder if there are empirically identifiable systematic brain differences associated with it and if these associations are contextualized within a scientifically robust theoretical understanding of the relationship between brain and behavior. I conclude by preliminary reflections on whether the issue of "mental disorder" versus "brain disorder" comes down to "the language of psychology" versus "the language of neuroscience," and the degree to which the former can be expressed in the latter.

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In *Are Mental Disorders Brain Disorders?* (Jefferson, 2022), Anneli Jefferson not only offers an extraordinary philosophical clarification of the notion of "brain disorder" as it applies to psychiatric conditions but also advances the debate by offering a new conceptual solution. A precis of the book has been published in *Philosophical Psychology* (Jefferson, 2023) and she has also previously presented the core argument in *Synthese* (Jefferson, 2020). Jefferson aims to answer the question of whether there is a legitimate philosophical sense in which mental disorders can be classified as brain disorders. Jefferson believes that mental disorders can be classified as brain disorders if they involve "dysfunction" in the brain, however, what is innovative about Jefferson's account is that the characterization of the brain processes as dysfunctional can be derived from the psychological dysfunction that they realize. In this commentary, I offer a brief overview of her central thesis, and then propose my own modified account of when we are justified in calling

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mental disorders as “brain disorders.” In doing so, I draw on recent work in neuroscience that understands the relationship between brain and behavior in complex, dynamic, and computational terms.

1. Narrow and broad views of brain disorder

Jefferson begins by examining two opposing views of brain disorders. The “narrow view,” championed by Thomas Szasz and others, sees brain disorders and mental disorders as fundamentally different. It takes neuropathological conditions such as neurosyphilis and Parkinson’s disease to be paradigmatic, and according to this view, the dysfunction in the brain must be identifiable independently of the psychological symptoms for the condition to be classified as a brain disorder. Additionally, the dysfunction must causally precede mental symptoms, and treatment must directly target the brain through medication or surgery, rather than indirectly through talking therapy. Under this view, some “organic” psychiatric disorders may be classified as brain disorders, but paradigmatic mental disorders such as schizophrenia, depression, or addiction would not be classified so. The narrow view is inadequate for Jefferson because both the etiology and treatments of mental disorders involve causal factors and mechanisms across multiple levels of organization, and the involvement of brain processes is poorly accounted by the narrow view. Furthermore, similar to psychological dysfunction, the characterization of somatic dysfunction is also dependent on the negative effects that a structural or functional anomaly has on the functioning of an individual. Based on these considerations, Jefferson concludes that there is no good reason that the narrow view should be considered a suitable and adequate standard for brain dysfunction in psychiatry.

The other position is a broad “brain-disorder-by-metaphysical-fiat” view. Since all mental states are *realized* by the brain, if there is something wrong in the mind, so the proponents argue, it follows that this dysfunctional mental process must somehow be realized by the brain. “Whatever is going on in the brain that is producing dysfunctional psychological processes must itself be dysfunctional, so the thinking goes. Led by this kind of reasoning, we even get psychiatrists asserting that to deny that mental disorders are brain disorders implies a form of dualism, positing minds and brains as separate entities and allowing spooky souls back into the picture.” (Jefferson, 2021)

Jefferson offers two main objections to this broad view. One is that “there may be different standards for what counts as pathological at the level of the brain and at the level of the mind. It is theoretically possible to say that the brain is functioning as it should, but things have gone wrong at the level of the mind.” (Jefferson, 2022) (p31) What is distinctive about mental disorders *as disorders* is lost in translation from the mental to the neurological, and what is left is a mere commitment to the physicalist worldview.

The second is that the phenomenon of multiple realizability has practical consequences that limit the utility of a broad notion of brain disorder. Multiple realizability refers to the idea that one and the same psychological state can be realized differently by different brain states. In extreme cases of multiple realizability, we can't tell the difference between the brains of people with a certain psychological problem and the brains of people who don't have that problem: "In other words, if psychological dysfunction is very variably realized in different people's brains (or indeed, in the brain of one person over time), then calling the associated brain states or processes disordered is of no practical use whatsoever." (Jefferson, 2022) (p35) Jefferson emphasizes the utility argument at another point: "Unless we have an identifiable brain difference which is sufficient for brain dysfunction, we lack *a scientifically useful feature that would justify speaking of brain disorders*. We would instead be in the situation where the only reason we have for calling these brains disordered is a metaphysical commitment to physicalism together with the claim that the property of being disordered is inherited across levels of description." (Jefferson, 2022) (p36) (my italics) Jefferson thinks that such considerations are also implicit in projects like the Research Domain Criteria (RDoC) (Morris et al., 2022): systematic brain differences have to be demonstrated by empirical research. It is an open question, not something to be assumed.

2. A derivative view of brain dysfunction

Jefferson's goal is to describe a concept of brain disorder that avoids the problems of both the narrow view and the broad view. Following the harmful dysfunction account of disorders (Wakefield, 2007), Jefferson adopts a notion of brain disorder that requires both "brain dysfunction" as well as "harm." In the context of mental disorders, Jefferson defines "brain dysfunction" as identifiable brain differences that realize mental dysfunction. It is notable here that while Jefferson does endorse Cummins's account of function/dysfunction (taking dysfunction to be "the failure of a trait or mechanism to contribute in the usual way to a system level capacity the organism has" (Jefferson, 2022, p. 5)), this account of dysfunction is poorly integrated with her overall view of mental disorders as brain disorders; a consequence of this relative lack of integration, a consequence we may even consider to be a strength, is that the central argument of the book is compatible with a wide variety of accounts of "dysfunction" (more on that later).

An important aspect of Jefferson's view is that this makes the notion of brain dysfunction dependent on the presence of psychological dysfunction: "brain differences underlying mental disorders derive their status as disordered from the fact that they realize mental dysfunction and are therefore

non-autonomous or dependent on the level of the mental.” (Jefferson, 2020) For psychiatric conditions, the hard work of figuring out whether something is a “disorder” or a “normal variation” or a “problem in living,” etc., still has to be done in psychological terms. Merely pointing to a systematic brain difference won’t settle that question. “. . . on my account we will often only be able to identify anomalies in brain processes as dysfunctional because they realize psychological dysfunction. In short, my aim is to mentalize the brain, rather than using the brain disorder label to discount the level of the mental.” (Jefferson, 2022) (p7)

A preliminary impression may be that finding systematic brain differences in instances of psychopathology should be easy enough, but Jefferson makes it clear that she is aiming for more stringent criteria. This is how Jefferson defines brain dysfunction: “*It is sufficient for X to be a dysfunctional type of brain process if tokens of this type always realize a psychological dysfunction.*” (Jefferson, 2022) (p39, italics in original)

Here’s an example she discusses:

“Assume, for the sake of argument, that we find differences in the dopamine system in addiction that underlie the cravings for the drug that we are familiar with on the psychological level and that we have characterized as dysfunctional psychological processes. There is promising research in this area. *Let us further assume that these differences in brain function are sufficient for the cravings, that we will not find this kind of brain difference without cravings. This means that this pattern of brain function realizes cravings.* In other words, it fulfils the condition of being sufficient for mental dysfunction and realizing that dysfunction specified above. This would then be a case where a mental dysfunction is also a brain dysfunction.” (Jefferson, 2022) (p 40) (my emphasis)

3. The realization of psychological dysfunction and systematic brain differences

To explore the linkage between “brain differences that realize a psychological phenomenon” and “brain dysfunction that realizes a psychological dysfunction” and the implications for Jefferson’s account, let us identify two distinct but related questions:

- (1) When are we justified in extending psychological norms/standards, by which we decide that psychological processes are not operating *as they are supposed to*, to the brain? That is, when are we justified in characterizing a brain difference as “dysfunctional” with reference to psychological norms?
- (2) When are we justified in characterizing a psychological condition as a brain condition?

Jefferson's answer to both justification questions is that an identifiable psychological condition must be realized by an identifiable brain state. The condition must correspond to a brain difference that we can *identify*, and this brain difference must be *sufficient* for the psychological difference to be experienced or observed. The brain difference identified must *always* be accompanied by the relevant psychological state. In such a scenario we are justified in extending the notion of dysfunction based on psychological norms (of irrationality, disproportionality, severity, etc.) to the brain processes, provided we recognize that the status of brain differences as dysfunctional is *derived* from the mental.

It is an important question: *why* do we insist on distinguishing between mental disorders and brain disorders in the first place? As argued by Matthew Broome and Lisa Bortolotti, mental disorders have “distinctive features [that] can be adequately characterized only by using the vocabulary of the mental. We do not deny that psychiatric disorders can be described as disturbances of neurobiological mechanisms, but we insist that they are pathological in virtue of their manifestations, and they manifest as disturbances of the mind.” (Broome & Bortolotti, 2009) It is this distinctive aspect of psychiatric disorders – they have features that can be adequately characterized only by using the vocabulary of the mental – that has to be acknowledged and respected by any account of mental-disorders-as-brain-disorders. The status of psychiatric disorders as *mental* disorders is secure, if and when we are justified in characterizing them as brain disorders. This applies even to the “narrow view” of brain disorders when a neuropathological process produces psychiatric symptoms, for example, Parkinson's disease psychosis. Parkinson's disease psychosis is *both* a mental disorder and a neurological disorder. It is a mental disorder because the clinical presentation and experience of psychosis “can be adequately characterized only by using the vocabulary of the mental” and it is a neurological disorder, because the central etiology is the loss of nigrostriatal dopaminergic innervation that characterizes Parkinson's disease.

In my view Jefferson is right to explore a notion of brain disorder where brain dysfunction is explicitly dependent on psychological dysfunction, and her articulation of this notion allows for the mental disorder – brain disorder debate to advance by breaking the impasse between the narrow and the broad views. However, the requirements of realization and sufficiency strike me as quite arduous to satisfy, to a point where I am uncertain that they can be practically met for any paradigmatic mental disorder.

One question that requires clarification is whether the realization relationship commits Jefferson to maintain that the psychological dysfunction is “nothing over and above” the brain dysfunction. Such an understanding of realization, for example, has been articulated by Shoemaker: “The relation between a realizer and what it realizes is

a constitutive relation – the having of a realized property consists in the having of whatever property realized it on that occasion. The occurrence of realized states is ‘nothing over and above’ the occurrence of their realizers.” (Shoemaker, 2007) (p 2)

The notion that a psychological state X is *nothing over and above* a brain state Y suggests a sort of identity relationship that has long been disputed by many in philosophy of mind, and these objections extend beyond concerns of multiple realizability. Tuomas Pernu, for example, argues that “if you hold the mental identical with the physical – as you should if you subscribe to the thesis of metaphysical physicalism – you are not automatically committed to holding the mental identical with, or reducible to, the brain. What this entails, to be precise, is that minds and mental states must extend beyond the brains and neural states they are conventionally attributed to . . . Mental states and processes are not items or substances, be they physical or mental, but functional capabilities: they enable agents to operate in larger environmental contexts.” (Pernu, 2021) Philosophers such as Sanneke de Haan have posited psychological processes to be in a mereological relationship with neurophysiological processes in the context of an organism in interaction with the environment (de Haan, 2020), and if the physiological and the experiential are two different ways of looking at, or zooming in on, an organizational process, then it is not quite accurate to say that the psychological processes are “nothing over and above” the neurophysiological processes.

A plurality of realization relations have been described in philosophical literature (Baysan, 2015) and it is not quite clear what exact notion of realization Jefferson has in mind. It may be the case, however, that all Jefferson means by realization in this context is that a psychological state is enabled by, or made possible by, a brain state (without any commitment that the psychological state is *nothing over and above* the brain state) and that this brain state is sufficient for the psychological state to occur.

Another worry I have in this regard is that it is very difficult to demonstrate that a brain difference is *always* accompanied by a psychological state. We have not been able to demonstrate such a relationship even for bona fide brain disorders such as Alzheimer’s disease and Parkinson’s disease. Brain changes such as amyloid and tau deposition aren’t even sufficient for cognitive impairment, let alone disturbances in mood and perception that are often seen in Alzheimer’s. Have we demonstrated what brain differences *realize* psychosis in Parkinson’s disease psychosis? In cases such as Parkinson’s disease psychosis, we do possess a causal explanation that links brain pathology with psychological signs and symptoms, but the sufficiency requirements for realization appear to be more stringent than establishing a causal relationship.

It is worth pointing out that even for conditions like Huntington's disease the requirements of the pathological change being sufficient and always associated with clinical presentation of interest aren't met. There are many forms of Huntington's disease mutations that have reduced penetrance, with CAG repeat length 36–38 apparently having penetrance as low as 6–20% (Kay et al., 2016).

What if we identify consistent brain differences but they are associated with a psychological dysfunction only 70% or 80% of the time? Or what if we identify consistent and systematic brain differences but only at the group level and not at the individual level? A classic example of that would be schizophrenia, where elevated *in vivo* markers of presynaptic striatal dopamine activity have been consistently reported, and the elevation in dopamine synthesis capacity shows a large effect size (Howes et al., 2012, 2013). This is a substantial, reliable, and systematic association, but it falls short of the brain difference being *sufficient* for psychological dysfunction.

What are we to make of such empirical findings? This is not the anarchy of extreme multiple realizability where no differences are identifiable, and this is not the sufficient realization relationship that Jefferson has in mind. I propose that we can consider the following as another Goldilocks solution to the justification question: we are justified in calling a psychological dysfunction a brain dysfunction if there are substantial, reliable, and systematic brain differences associated with the psychological dysfunction.

4. Recent developments in neuroscience

We can't talk about what a brain disorder is and how psychiatric disorders might be brain disorders without taking into account how neuroscientists understand the relationship between brain and behavior. Many neuroscientists have challenged long-standing assumptions of the field in recent years, and these include assumptions that are relevant to the “are mental disorders brain disorders” debate. Luiz Pessoa's latest book, *The Entangled Brain* (Pessoa, 2022a) illustrates these developments in neuroscience quite well. Pessoa summarized the main thesis of the book for an article in the *Journal of Cognitive Neuroscience* (Pessoa, 2022b), which I am using as my reference. “Entangled” refers to the dynamic and highly context-dependent interactions of different brain regions. Pessoa understands the brain as a complex system where organizational relationships and dynamic interactions lead to novel collective properties. He invokes 3 principles of brain organization:

- (1) massive combinatorial anatomical connectivity
- (2) highly distributed functional coordination
- (3) networks/circuits as functional units

I propose that this general architecture supports a degree of computational flexibility that enables animals to cope successfully with complex and ever-changing environments . . . Anatomy provides a backbone that constrains function, but the structure – function relationship is anything but simple . . . the relationship between signals in disparate parts of the brain is not determined by structural pathways in a straightforward manner . . . In general, mental processes of interest cut across domains and do not respect putative boundaries between traditional systems (e.g., emotion, cognition). In fact, crisscrossing anatomical/functional connectional systems dissolve potential lines of demarcation. (Pessoa, 2022b)

Let's consider another recently published article: "Improving the study of brain-behavior relationships by revisiting basic assumptions." (Westlin et al., 2023) Westlin et al. challenge 3 traditional assumption of brain-behavior relationships, such as the assumption that psychological categories can be localized to dedicated brain regions/networks and that there can be a one-to-one correspondence. Instead, they argue that psychological states arise from activity across the entire brain, the relationships between neural ensembles and psychological states are degenerate (many-to-one) and that "Mental events emerge as a complex ensemble of signals: an instance of a psychological category emerges from a complex ensemble of signals from the brain, body, and world. These signals can only be understood in relation to the rest of the ensemble; i.e., each may have a weak effect on its own, but a strong effect when considered collectively." (Westlin et al., 2023)

The paper has generated a lot of debate in the neuroscience community. In this context, the neurogeneticist Kevin Mitchell commented on twitter:

"IMO [In my opinion], some pushback against *simplistic* ideas of function localisation is reasonable (though I think the field has moved on from 'blobology,' to be fair). By simplistic, I mean taking brain region A to "do X" (based on activity patterns or lesion info), which seems to imply *sufficiency*, not just *necessity*. There's an analogous pitfall in genetics with the common construction: a "gene for X" (as opposed to the more careful: a gene required for X). However, that caveat doesn't invalidate the specificity of activation patterns and connectivity and lesion effects, etc., that support differential involvement of brain structures in different functions. And the fact that such functions heavily rely on interconnectivity and can be modulated by all sorts of contextual information doesn't mean it's some kind of neural free-for-all." (Mitchell, 2023)

How do these neuroscientific debates inform the question of whether mental disorders are brain disorders? For me, they jeopardize Jefferson's insistence on the criterion of *sufficiency*, that a dysfunctional type of brain process should always realize a psychological dysfunction. The problem is that if neuroscientists such as Pessoa, Feldman Barrett, and Mitchell are correct, this stringent criterion of sufficiency is impossible in practice. Our best neuroscientific understanding of the brain-behavior relationship tells

us that this sort of sufficient one-to-one correspondence, as a matter of general principle, is going to be the exception rather than the rule. An account of brain disorders that fails to take this into account just isn't going to be very useful. And utility matters here, since one of the main arguments by Jefferson against the broad metaphysical view is the lack of scientific usefulness. If we want a scientifically useful notion of mental-disorders-as-brain-disorders, we have to work with what neuroscience tells us about the relationship between brain and behavior (Aftab & Sharma, 2021).

A philosopher could maintain that it is theoretically possible for a difference in brain states to always realize a difference in psychological states, if we possess an absolute and perfect knowledge of each and every detail of the brain states involved (à la Laplace's demon), such that even the knowledge of the influence of past brain states and knowledge of contextual influence from the body and world is somehow taken into account. Even if this were true, and I'm not certain that it is true, such total and perfect knowledge of brain states is inaccessible to us.

What can we reasonably expect? Similar to Mitchell, I think we can expect differential involvement of brain functions in different psychiatric disorders, expressed, for example, with reference to brain networks and their dynamic activity, or even expressed in neurocomputational terms. These associations may not be necessary or sufficient; they may not even be highly specific. But they can be systematic, substantial, and reliable, and allow for the increased neuroscientific understanding of the etiology of mental disorders and better development of neurotherapeutics.

There is an element missing, however, in my proposal that we can consider psychiatric disorders as brain disorders if they are associated with substantial, reliable, and systematic brain differences. Even for *normal* psychological phenomena, establishing specific and sufficient relationships is an elusive goal. For example, consider Feldman Barrett's assertion about the neurobiology of emotions: "Even after a century of effort, scientific research has not revealed a consistent, physical fingerprint for even a single emotion." (Barrett, 2017) (p 11) Yet, it would be odd to debate, as is sometimes debated in the case of psychiatric conditions, whether emotions have a basis in the brain. Even if we cannot identify a brain state that *always realizes* an emotion, the brain-based nature of emotions is not in dispute. Scientists instead focus on how to best formulate and theorize the relationship between emotions and the brain. The relationship is such that it involves many areas of the brain, there is no one-to-one mapping, and emotions emerge from a computational process that involves complex dynamic interactions in a highly context dependent manner (Barrett, 2017). This theoretical framework of the brain-behavior relationship is crucial for mental disorders as well.

This, in my opinion, is the crux of the mental-disorders-are-brain-disorders project: a psychiatric disorder can be said to be a brain disorder if there are empirically identifiable systematic brain differences associated with it and these associations are contextualized within a scientifically robust theoretical understanding of the relationship between brain and behavior.

Consistent with the spirit of Jefferson's account, this is still an empirical matter. It is an open scientific question whether this goal will be achieved and for which conditions. It is also a goal that meaningfully aligns with the research agenda of biological psychiatry and frameworks such as the RDoC. And it reminds us that the question of the neurobiological basis of psychopathology cannot be divorced from a broader neuroscientific understanding of the brain-behavior relationship.

5. Dysfunction

There is considerable disagreement over what should count as a "dysfunction" when it comes to mental disorders. Candidates range from common-sensical, folk psychological notions to more precise definitions in evolutionary terms (Aftab & Rashed, 2021). There are also notions of "disorder" that invoke no specific sub-concept of "dysfunction" (Bolton, 2008). Pragmatist, non-essentialist accounts of psychiatric classification have also gained prominence in psychiatry over time (Aftab & Ryznar, 2021). As noted previously, despite Jefferson's expressed commitment to Cummins's account of dysfunction, a curious advantage of her account of mental disorders as brain disorders (and my derivative one) based on identifiable brain differences is that it is compatible with a wide range of notions of psychological dysfunction. We can sidestep that debate almost entirely. The basic requirement is that there ought to be identifiable differences in the brain that realize a particular psychological state that we have characterized as a psychological dysfunction. Whether such identifiable brain differences exist or not for a particular psychological state is independent of whether we call that psychological state a dysfunction or not.

6. Brain disorders and the language of neuroscience

Another consideration is that our contemporary notions of "brain disorder" may be revised in the light of on-going work in the area of computational neuroscience and computational psychiatry. Neuroscientists increasingly conceptualize the brain as a predictive organ – the so-called "Bayesian brain" – and under such a view: "psychopathology represents false inference or aberrant belief updating, under a view of the brain as a statistical organ, generating predictions and revising its (subpersonal Bayesian) beliefs on the basis of prediction errors. Crucially, these predictions are contextualized with predictions of

precision or predictability that instantiate attentional or intentional set; allowing the selection of attenuation of prediction errors via a process of precision weighting. This precision weighting is nothing more than modulating the gain, postsynaptic sensitivity or excitability of appropriate neuronal populations.” (Friston, 2022)

If, for instance, it can be demonstrated that a particular mental disorder arises from aberrant belief updating, debating whether it is or isn't a “brain disorder” would be largely a moot point, even if there are no neuroanatomical or neurophysiological markers consistently and specifically associated with it. Systematic brain differences that characterize a mental disorder or a particular psychological condition may very be expressible in computational terms.¹

More importantly, however, the development of computational psychiatry is reflective of the theoretical evolution of neuroscience. In some ways perhaps, the issue of “mental disorder” versus “brain disorder” comes down to the language of psychology – ordinary as well as clinical – versus the language of neuroscience, and the degree to which the former can be expressed in the latter. In the past, neuroscience has been limited by methods available (e.g., structural and functional neuroimaging), but the embrace of complex systems, network theories, and computational approaches opens up new possibilities of translation. Such a neuroscience would have to meaningfully tackle mental phenomena such as consciousness, intentionality, agency, and normativity, and we are not quite there yet. The fundamental motivation behind “mental disorders are brain disorders” may be something as simple as: one day we will describe, explain, and understand mental disorders using the language of neuroscience. The key limitation is that it cannot simply be assumed that this scientific undertaking will be successful. The relationships may be far too complex to be tractable – we only have to look to genetics to appreciate that – and neither confidence nor faith will serve us well. Jefferson's work is a powerful reminder that a metaphysical commitment to physicalism is not an adequate justification for us to call mental disorders as brain disorders. There are several ways in which a better justification might be worked out; Jefferson offers a justification based on realization and sufficiency, and I've offered answers of my own to the justification question, but we are united in the sentiment that an empirical demonstration is necessary. Neuroscience has to actually deliver the goods and show us the receipts.

Note

1. I recognize that my reflections here on the implications of computational psychiatry for the debate around mental-disorders-as-brain-disorders are under-developed. This is partly due to lack of space, and partly because the field of computational psychiatry is itself so nascent and so under-theorized that the remarks I offer here are by necessity premature.

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