Are Mental Disorders Brain Diseases, and What Does This Mean? A Clinical-Neuropsychological Perspective

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Brain disease · Mental disorder · Clinical neuropsychology · Biological psychiatry

Abstract
Neuroscientific research has substantially increased our knowledge about mental disorders in recent years. Along with these benefits, radical postulates have been articulated according to which understanding and treatment of mental disorders should generally be based on biological terms, such as neurons/brain areas, transmitters, genes etc. Proponents of such a ‘biological psychiatry’ claim that mental disorders are analogous to neurological disorders and refer to neurology and neuropsychology to corroborate their claims. The present article argues that, from a clinical-neuropsychological perspective, ‘biological psychiatry’ is based on a mechanistic, ‘cerebrocentric’ framework of brain (dys-) function which has its roots in experimental neuroscience but runs up against narrow limits in clinical neurology and neuropsychology. In fact, understanding and treating neurological disorders generally demands a systems perspective including brain, organism and environment as intrinsically entangled. In this way, ‘biological’ characterizes a ‘holistic’, nonreductionist level of explanation, according to which the significance of particular mechanisms can only be estimated in the context of the organism (or person). This is evident in the common observation that local brain damage does not just lead to an isolated loss of function, but to multiple attempts of reorganization and readaptation; it initiates new developments. Furthermore, treating brain disorders necessarily includes aspects of individuality and subjectivity, a conclusion that contradicts the purely ‘objectivist’, third-person stance put forward by some proponents of biological psychiatry. In sum, understanding and treating brain damage sequelae in the clinical neurosciences demands a biopsychosocial perspective, for both conceptual and historical reasons. The same may hold for psychiatry when adopting a brain-based view on mental disorders. In such a perspective, biological psychiatry seems an interesting project but falls short of its original claims.

Introduction
Psychiatrists and psychotherapists are increasingly faced with neuroscientific research findings on mental diseases. Along with the benefits of this research, far-reaching claims are raised that our concept of mental illness must be fundamentally revised [1–4]. Mental diseases, so claims go, ‘should be understood and treated as
brain disorders’ [4, p. 2221]. Although such statements seem to promote profound, almost revolutionary changes, their implications remain mostly indefinite. At least, some common assumptions may be deduced: as neuropsychology and experimental neuroscience have found that mental functions are specifically located in the brain, mental dysfunctions may be traced back to abnormal brain areas as well, at least in principle [1, 3, 5]. As brains are supposed to ‘generate’ mental abilities, they also ‘generate’ mental disorders [3, p. 229], due to defective computational principles [5]. Therefore, the brain alone is the place to look for pathology even in cases in which environmental factors are important as the latter should ‘materialize’ in the brain as well [1]. This may also allow eliminating all kinds of speculative psychological theorizing in favor of ‘hard science’ [3, p. 65] and diagnosing diseases and evaluating therapeutic outcome in ‘objective’ ways (i.e. by relying on biomarkers [1, 6]). Clinical neurology and neuropsychology provide points of reference for how psychiatry should develop in the future [4, 7].

Opponents of biological psychiatry often dispute commonalities between the two disciplines, psychiatry and neurology. They e.g. emphasize the phenomenological, subjective approach in psychiatry, which they find largely irrelevant in neurology (as in the rest of medicine; see Banner [8], Paris [9] and Graham [10]). Furthermore, whereas neurology allegedly deals with ‘brute, mechanical’ [10] lesion-deficit associations [9], psychiatry – in contrast to the rest of medicine – is claimed to need a higher level of description in order to adequately define mental illness: ‘the person, within their environment’ [8, p. 511; see also 9]. It is even feared that biological approaches to psychiatry may eliminate the possibility of psychotherapeutic treatment [9, p. 514] in favor of ‘direct’ (e.g. pharmacological) manipulations of brain activity.

Flying a ‘biological’ flag has hardly led to practical consequences for psychiatry so far. For instance, no single biomarker has become a diagnostic criterion for any mental disorder (except for dementia) in the development of the recent DSM-5. However, this shall not be the focus of the present article which aims at conceptual issues. From a clinical-neuropsychological perspective, I argue that many proponents of biological psychiatry (and many of their critics alike) seem to share a mechanistic, cerebrocentric viewpoint of clinical neurology and neuropsychology which runs up against narrow limits. In fact, a ‘brain’ perspective will have much less revolutionary implications for psychiatry than expected.

How Brain Disorders Are Understood and Treated – A Case Example

Let me first present a sketchy neuropsychological case vignette that reveals a range of issues in the diagnosis and treatment of brain lesions. Edith, a 44-year-old mother of two small children, has undergone surgery for an extensive brain tumor in the left frontal lobe, an astrocytoma, which has been completely removed. Edith seems quite appropriate in her conduct at our first visit. A comprehensive neuropsychological test battery reveals below average results in basic reaction speed and verbal fluency. All further tests (verbal and figural memory, selective and divided attention, general intelligence, spatial and executive functions such as planning, flexibility and interference) reveal average results. Neither Edith nor her family has noticed any consequences concerning the two areas of deficit (i.e. reaction speed and word fluency). However, Edith complains that she is now more easily distracted, though all tests assessing this ability have revealed average results. Her husband also reports that she has now more problems in making decisions in everyday life, in her ‘former life’ she had been ‘much more resolute’. No further cognitive impairments in everyday life have been observed. Edith has returned successfully to her job as an accountant, though on a part-time basis as she had started experiencing fatigue soon after returning home. However, she feels deeply unsettled and hopeless, withdraws from other people, including family and colleagues. Her husband cannot understand her mood swings. Things could have come out much worse, he says. Edith, however, thinks of herself as a victim of another stroke of fate after recalling several other traumatic life episodes.

Neuropsychological therapy does not address verbal fluency deficits at all as they do not have any bearing on Edith’s everyday life. Reaction speed is trained in a computer-based setting as it is relevant for driving a car. Although tests did not ‘objectify’ distraction problems, strategies how to avoid or minimize distraction at home and in her job are developed and practiced, according to Edith’s complaints. Most of the remaining sessions are devoted to her emotional problems, to promoting self-confidence and self-esteem and to developing motivating new life goals (such as caring for her little daughters and finishing the education which her father had forbidden to her earlier). This includes sessions together with her husband, in order to convey information about the changes and to foster empathy. The treatment turns out to be successful for both Edith and her family.

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The Brain as a System (within a System)

A point that seems to make neuroscience attractive for biological psychiatrists is the idea that different aspects of mental functions can be reliably associated with specific brain areas, as revealed by neuroimaging experiments in healthy subjects or by lesion-deficit correlations in neurological patients [1, 3]. This is a very important point as it is tied to the claim that local abnormalities in the brain ‘produce’ specific symptoms of mental disease [3, p. 240]. From this perspective, it seems most surprising that Edith’s relatively large left-frontal tumor led to only a few below-average test results, seeing the variety of tasks that elicit left-frontal brain areas in functional imaging [11, 12]. Although it does not follow that all brain areas are functionally identical, the view of a highly compartmentalized brain [3, p. 87] largely results from experiments which relate differences between experimental conditions to regional brain activations. If interpreted uncritically, these studies lead to an inadequate localizationist view of the brain [13], as they e.g. do not account for the fact that the brain can reorganize and compensate damage, at least to some extent. Compensation can only be studied in cases in which the brain’s normal functioning is disturbed, which is normally not the case in experimental investigations in healthy subjects.

Interestingly, mechanical metaphors are often put forward in order to explain mental disorders neuroscientifically. For instance, it is suggested that as soon as we have identified relevant brain mechanisms, specific drugs can be designed to target specific docking sites in order to treat a disorder in a similar way than a piano tuner retunes a particular string which went out of tune [3, p. 14]. Certainly, I do not want to suggest that these authors view the brain as a device as simple as a piano. The point, however, is not simplicity, but the idea that the brain has systemic properties, in profound contrast to the piano. Time seems a relevant parameter here, as fairly impressive functional reorganization can be observed in the case of developing tumors [14], in contrast to more abrupt lesions such as strokes, although compensation takes place here as well, as e.g. the phenomenon of ‘silent strokes’ shows [15]. Such phenomena challenge localizationist approaches in general. Thus, there is not only the problem that differences in the brain of psychiatric patients and controls do not have to reveal much about the causal role of the respective structures [16], the more serious question is under which conditions such differences can or cannot be compensated for.

One might object that deficits of ‘frontal’ functions might be more salient in cases other than Edith’s. This is certainly true, but it does not eliminate the problem, it puts up another one: the striking interindividual variability with respect to the outcome in comparable brain lesions. Numerous studies e.g. on neurodegenerative disorders have revealed a variety of intraorganismic or intrapersonal factors, such as brain volume, education, socioeconomic status, education, etc. [17, 18] which influence the course of the disease. Adding to this, cerebral reorganization processes can later be complemented by individual coping strategies, such as: avoiding difficult situations versus actively training them, neglecting problems versus overemphasizing them, different ways of compensating impairments, etc., depending on a variety of neurological, psychological and social factors, leading to quite different clinical pictures. Lesion-deficit correlations can help guiding assessment and therapy, but they are highly simplified heuristics. They do not adequately capture the complexity and individuality of brain lesion outcomes which neuropsychologists can only assess by integrating a range of sources of information (psychometric tests, behavioral observations, interactions with the patient, patient’s and caregivers’ reports, etc.).

Are Brain Disorders Just inside the Brain?

Obviously, brains have adaptational capacities, and a crucial aspect of all types of adaptation is that they cannot be understood without the environment in relation to which adaptation takes place. A purely brain-inherent view of mental (dys)functions is therefore inadequate. Thus, we have to refer to a broader, systemic perspective, including brain, organism and environment, or, in other words, brain-person-milieu [19, 20]. Brain diseases are ‘transcerebral’, both conceptually and clinically. They are not ‘brute mechanical’ [10, p. 103]. Edith’s fatigue may demonstrate this point: fatigue is a frequent, highly disabling consequence of a range of neurological conditions, including brain tumors [21]. It usually presents in a complex clinical picture, resulting from an interaction of physiological, psychological and psychosocial factors, such as the brain lesion, stress, medical treatment, cognitive dysfunctions, mood, sleep disturbances, lack of social support, etc. [22]. Fatigue is often underdiagnosed in acute neurological treatment as it may become apparent only in complex, highly stimulating everyday life situations with numerous sources of distraction and multitasking [23]. Such a ‘holistic’ per-

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spective adequately captures how clinical neuropsychologists actually understand and treat brain diseases, instead of overemphasizing a lesion-deficit view [13]. An out-of-tune piano string is a suggestive but highly misleading metaphor. Why should this be different in mental diseases?

The problem might become even clearer when we turn to the disease concept of biological psychiatry, which mostly comes down to 'brain abnormalities' in the sense of some kind of statistical deviation. This puts up the question whether such a deviation can define a disease or deficit, a position that many psychiatrists (and neurologists, too) seem to defend [3, p. 151; 4, p. 2224; 24, p. 341]. However, such a conclusion is problematic for several reasons. First of all, we would have to define the amount of deviation until a pathological state is diagnosed. How could such criteria be developed? This would already presuppose an independent definition of 'pathological'. 'Deviance' puts up the question that it is supposed to answer; the explanans turns out to be the explanandum. Second, which is the 'correct' reference that allows defining (ab)normality? The brain is not a tool box which provides universal, 'natural' cognitive and affective functions. Its functions rather develop in an organism entangled with its particular physical and sociocultural environment. No brain 'abnormality', structural or physiological, has any bearing on understanding disease outside this context. As an example, Hobson and Leonard [3, p. 151] refer to imaging studies showing 'abnormal neuronal circuits' in the orbitofrontal cortex in patients with obsessive-compulsive disorder and cite further evidence of commonalities between 'obsessive repetitions of OCD ... (and) ... repetitive magical and religious rituals in various cultures'. If we found actual similarities in brain circuits between obsessive-compulsive disorder patients in an industrialized society abnormally practicing rituals and people of an indigenous tribe normally practicing rituals – as the example suggests – would this not show that a brain-immanent perspective has no bearing on the question of normality? In clinical neuropsychology, it can be quite difficult to find the appropriate distribution to which individual test scores can be compared [25], especially if patients from different sociocultural, socioeconomic, educational and linguistic backgrounds are assessed. However, neuropsychologists are actually much less interested in the statistical deviation per se, as this is only a makeshift which serves as an estimate for the premorbid status of the individual patient (as premorbid data are rarely available). In other words, what is truly at stake is the comparison between the abilities of one and the same individual before and after the incident. We need an individual reference. This becomes evident in Edith's case: although Edith showed average results in tasks measuring cognitive distraction, she complained about an increased distractibility in comparison to her premorbid state and with respect to her everyday life. It seems noteworthy that such an intrindividual perspective is already inherent in the definition of dementia as a mental deterioration of a person relative to prior abilities [26]. Last but not least, focusing on interindividual comparisons is a frequent reason for conflicts between patients and physicians in many areas of medicine in clinical practice: patients may perceive their physicians as not being empathic, as they experience changes on an individual basis and relative to their living situation, whereas physicians often stick to the traditional medical model which is based on general statistical distributions of interindividual comparisons.

All this leaves the question of pathology still unanswered! Proponents of biological psychiatry claim that brain science (as 'hard science' [3, p. 211]) can give us exhaustive scientific, 'objective' definitions (in terms of abnormal parameters) of whether someone is mentally ill, and, accordingly, whether treatment was successful [1, 3, 6]. But what about all those anatomical or physiological deviances which are not seen as being pathological? This phenomenon is expressed in the medical term of 'norm variant', which is also found on the level of brain structure [8, 13]. Deviance can therefore never define disease or disorder, and it is all the more surprising that this problem seems to find so little attention in biological psychiatry. And if we agree that abnormality cannot define disease, how could normality define therapeutic success? Medicine does not exist because some bodies deviate from the rest, but because people suffer, that is they experience pain or discomfort, fear death, feel overly limited in what they want to make out of their lives etc. Or even: they do not conform to standards of the sociocultural context they live in. Neuroscientific findings might help in clarifying diagnoses, but it seems hard to imagine how they could define that someone is ill (or healthy). Such a conclusion seems inseparable from an individual, subjective and situational judgment, and a judgment with respect to values [27]. In other words, it is considerably bound to factors which do not fall into the area of the natural sciences [13, 28], with their emphasis on objective and 'value-free' knowledge. In this respect, neurology and psychiatry are in fact alike (along with all other domains of clinical medicine).
Identity and Integrity as Biological Parameters

As illustrated above, brain damage does not just lead to losses of function, but induces systemic changes on multiple levels (brain-person-milieu). Changes are not only a matter of quantity, but also of quality. Brain damage initiates multiple cascades of downgrading and re-adaptation, conscious and unconscious, spontaneous and in longer terms. These processes seem to serve a common purpose: to establish a new stable state in the brain-person-milieu system to preserve as much of a person's identity as possible [20], 'to make the best out of' the remaining possibilities. In other words, lower-level properties of the system are oftentimes determined by its higher-level properties [29]. In terms of the piano metaphor, the piano string may give the same sound, irrespective of how the other strings are tuned. In a systems perspective, by contrast, the piano as a whole may attempt to retune not only the out-of-tune string, but the remaining strings as well, in order to establish a new sort of 'congruence', even if its general tuning might finally differ from other pianos. Biological systems are not only 'more than the sum of their parts', but they can regulate their parts [29]. This essential property seems hardly acknowledged in biological psychiatry. Many proponents explicitly seem to stick to a view according to which the role of isolated factors such as amygdala activity can be directly extrapolated to explain global organismic phenomena such as anxiety [1, 3, 5]. However, as empirical research shows, even the most 'elementary' emotions seem to be connected with complex, shifting networks [30]. Biological systems (such as brains or organisms) are obviously able to counteract perturbations to a considerable extent, thereby redirecting their parts (neurons, brain areas, etc.) in different ways and from different initial conditions [31, 32]. In contrast to the common 'bottom-up' view in the experimental neurosciences, such a perspective also allows addressing an interesting, but often neglected issue: why do brains/organisms not completely change from one moment to the next in the face of so many different stimuli in every second? Why (and how) do they maintain stability and integrity?

Top-down processes seem essential for understanding how biological systems produce order, and how they even stabilize states of order that are detrimental to themselves. This phenomenon is very important for understanding mental disorders, which are often distinguished by tendencies to interpret stimuli very selectively and to misinterpret even 'beneficial' stimuli in often grossly distorted ways. To come back to our case example: why did Edith feel not lovable although her husband told her the opposite every day? Why did she see herself as a victim although the tumor had been successfully removed? Obviously, she had developed a negative view of herself which now served as a pattern to interpret stimuli accordingly (very much like a 'schema', e.g. in the sense of Young et al. [33]). This helped her to maintain an identity, even a distorted one, one that served maladaptation. Accordingly, any treatment should aim at shifting the system into a new stable state. Speaking in terms of psychotherapy, it should modify existing schemas (sensu Young et al. [33]) rather than symptoms, and, with regard to the brain, systems rather than particular mechanisms.

How Biological Is Biological Psychiatry?

As we have seen, proponents of biological psychiatry tend to overestimate the explanatory significance of 'basic' factors such as genes, transmitters, neurons or brain areas. In other words, an analytic research strategy, such as in physics and chemistry, is transferred to living material. As living beings are not seen to exhibit specific, non-reducible ('holistic') properties, 'biological' eventually becomes a dispensable term. In fact, it would seem more appropriate to speak of 'physicochemical' instead of 'biological' psychiatry. In other words, biological psychiatry seems to define 'biological' in a way that is incompatible with how life is conceptualized by many modern approaches in biology. Thus, criticizing reductionism is a legitimate enterprise in psychiatry [9, 34] with a long tradition, but the same holds true for biology. In biology, reductionist claims have been convincingly criticized, at least with respect to the reduction of theories [35]; it has been argued that (i) one and the same elementary (e.g. molecular) process may have quite different effects on higher (e.g. physiological, developmental, organismic) levels depending on the context and that (ii) one and the same higher-level process may be realized by quite different kinds of lower-level processes [35]. Both issues are necessary to understand brain lesions, as argued above. On the other hand, medical treatment searches for more mechanistic, linear causal strategies, as these are straightforward to apply (and evaluate). Is there a way to reconcile both perspectives? A promising approach might be to allow for a mechanistic framework that relates phenomena (such as long-term potentiation and the hippocampus in memory) at different levels of explanation [36]. This strategy, which is a common practice in sci-
ence, uses the strengths of the mechanism concept, namely the establishment of causal relations between particular factors, but does not determine the nature of phenomena (i.e. whether biological entities are ‘nothing but’ collections of mechanisms) [35]. Furthermore, it is still open for modeling contextual influences. It seems to be a favorable idea especially with respect to clinical psychiatry to search for possibilities of influencing mechanisms on different levels (pharmacology, brain stimulation, cognitive training and psychotherapeutic techniques) and to relate them in order to maximize treatment possibilities. Such a pragmatic approach, however, is already the actual gold standard in many medical areas and has already guided research and therapy on mental disorders for a long time under the well-known term ‘biopsychosocial model’ [37]. Historically, an essential source of this model is the ‘general systems theory’ [38], the founder of which, the biologist Ludwig von Bertalanffy (1901–1972), had already regarded it as an integrative framework for psychiatry [38, 39]. It allows conceptualizing mental disorders [40] at different levels, ranging from subpersonal (brain, hormones, etc.) to suprapersonal (social-cultural) [41, 42]. Interestingly, some of Bertalanffy’s most important inspirations came from observations on brain-damaged subjects by the German neurologist Kurt Goldstein (1878–1965) [41] and his holistic, organismic foundation of clinical neurology and neuropsychology [13]. Goldstein [40] demonstrated how brain lesions induce global, qualitative changes in the whole organism (or person) in its attempts to establish a new balance with its environment. He was among the first to propagate a systems view of the brain on the basis of his clinical observations, although he nevertheless emphasized that linear lesion-deficit associations might be practically useful [13]. Goldstein [40] extensively described all the characteristics of brain damage that I have tried to apply to the claims of biological psychiatry in the present paper: the compensational abilities of the brain; the entanglement of brain/organism and environment; individual, qualitative and subjective aspects in the definition of disease/deficit; the question of practically significant goals and outcome parameters of treatment. In clinical practice, Goldstein emphasized the importance of milieu-based as well as of psychotherapeutic interventions for neurological patients [45], both of which are still essential in neuropsychological rehabilitation [46].

Neurology seems to appeal to biological psychiatrists because of its ‘organic’ disease concept and the fact that it treats diseases causally in the brain [3, p. 213]. This seems to cut the story too short, however. Take a severe CNS disease such as herpes simplex encephalitis as an example. In fact, acyclovir is effectively used to fight the virus within the brain. It is a good example for a causal and effective (live-saving) treatment. However, treatments rarely lead to a restitutio ad integrum. Long-term consequences of the disease have to be treated with a variety of other means (cognitive training, psychotherapy, etc.). It is increasingly acknowledged that a biopsychosocial perspective is crucial in the treatment of neurological diseases such as Parkinson’s disease [47, 48], multiple sclerosis [49, 50], post-stroke depression [51], epilepsy [52] or organic psychopathology in general [53, 54].

**Conclusion**

There may be good reasons why psychiatry could profit from the clinical neurosciences, but the common view that neurological diseases are exhaustively understood and treated on the basis of neurophysiological mechanisms seems obsolete. A biopsychosocial framework may be criticized for suffering from eclecticism and for not providing specific treatment options [55, 56], but this does not mean that we cannot decide between the different treatment options in specific cases on empirical grounds. If increasing neuroscientific research can help further elucidating the ‘bio’ part of mental diseases, potentially leading to new treatment options, this should be highly welcome. However, claims that commit us to a certain level of explanation from the beginning and to exclude all others a priori as being ‘unscientific’ (as they supposedly do not relate to the brain, see Hobson and Leonard [3, p. 77]), is neither conceptually adequate nor clinically helpful. It also relies on a misconception of how brain lesions are actually understood and treated. On the other hand, a biopsychosocial framework which has

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1 Goldstein’s use of terms such as ‘organism’ or ‘environment’ in the context of human beings seems unfortunate, as it wrongly suggests that he held a biologistic or naturalist stance. By contrast, Goldstein followed the ideas of his cousin Ernst Cassirer (1874–1945) who emphasized that humans have the inherent ability to use symbols in a very productive way [40], in contrast to animals. Thus, humans do not just inhabit environments, but actively create them in terms of language and culture. Furthermore, Goldstein conceived of human ‘environments’ as essentially social, constituted by personal relationships [40]. The latter idea became especially prominent in Goldstein’s late work on psychotherapy. Last but not least, it should be noted that, although Goldstein never referred to himself as a phenomenologist, he contributed to the development of phenomenology and phenomenological psychiatry in substantial ways. One way of contributing was through his impact on the works of the French phenomenologist Merleau-Ponty [43], but he influenced existentially oriented phenomenological psychiatry as well [44].
strong roots in clinical neurology and neuropsychology, still offers a pragmatic and patient-oriented approach. It enables a multitude of treatment options and acknowledges the significance of sociocultural contexts without which brain (dys)function can never be adequately understood.

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