Schizophrenia and the Dysfunctional Brain*

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Scientists, philosophers, and even the lay public commonly accept that schizophrenia stems from a biological or internal 'dysfunction.' However, this assessment is typically accompanied neither by well-defined criteria for determining that something is dysfunctional nor empirical evidence that schizophrenia satisfies those criteria. In the following, a concept of biological function is developed and applied to a neurobiological model of schizophrenia. It concludes that current evidence does not warrant the claim that schizophrenia stems from a biological dysfunction, and, in fact, that unusual neural structures associated with schizophrenia may have functional or adaptive significance. The fact that current evidence is ambivalent between these two possibilities (*dysfunction* versus *adaptive function*) implies that schizophrenia researchers should be much more cautious in using the 'dysfunction' label than they currently are. This has implications for both psychiatric treatment as well as public perception of mental disorders.

Keywords: *Mental disorder, mental illness, function, dysfunction, schizophrenia, natural selection, neural selection, psychiatry*

1. Introduction

Biologically-oriented psychiatrists rarely question that schizophrenia stems from a neurobiological 'dysfunction.' This dysfunction is often characterized by colorful and imaginative locutions: *The Broken Brain* is

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the title of a book on schizophrenia (Andreasen 1984), signifying that the schizophrenic brain is not in 'good working order' and needs to be 'fixed.' More eloquently, Heinrichs (2001) describes schizophrenia as the product of a 'neurochemical tempest':

> "Is schizophrenia really a kind of biological tempest, where tides of neurotransmitters crest and recede? Do substances with cryptic and unpronounceable names play havoc with patches of protein called receptors, and do they upset chemical balances in regions of the brain that control thought, feeling, and movement?" (ibid., 181).

Here, neurotransmission in schizophrenia is likened to a malevolent storm at sea, which reflects, and explains, the uncontrollable and chaotic 'storm' of thoughts and feelings associated with schizophrenia. This, again, reflects the view that 'all is not as it should be' in the schizophrenic brain.

Such expressions permeate not only literature for popular audiences, but scientific literature on schizophrenia as well. It is unusual to read a scientific article on the biological basis of schizophrenia that does not at some point characterize the schizophrenic brain as beset by a 'dysfunction,' 'failure,' 'disability,' 'aberrance,' 'malfunction,' 'deficit,' or 'excess.' All of these are clearly normative terms: they imply a norm, or standard, in relation to which the activity of the brain is assessed as deviant. Moreover, this deviance is not merely statistical, but normative in the proper sense, because it supports the notion that the schizophrenic brain is malfunctioning or dysfunctional and not just different or unusual. The assumption that the brain of the schizophrenic patient is not working 'as it ought' or 'as nature intended,' then, is central to biological approaches to psychiatry. Tacitly or explicitly, much biological research in psychiatry is fueled by the desire to identify what has 'gone wrong' in the schizophrenic brain or how nature has 'erred.'

Some philosophers and psychiatrists have even argued that mental disorders should be *defined* or conceptually analyzed in terms of these internal or biological 'dysfunctions' (Klein 1978; 1999; Spitzer and Endicott 1978; Wakefield 1992; 1999; 2007; Spitzer 1999; Nesse 2007). Some have suggested that such definitions be officially incorporated into professional

nomenclature and publications, such as the upcoming revisions of the World Health Organization's (WHO) *International Classification of Diseases* (ICD) and the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (Rounsaville et al. 2002; First 2007). Doing so would have significant implications both for the developing self-conception of psychiatry as well as for public perception, because it would canonize the view that the chief aim of professional psychiatry is to identify and correct these internal dysfunctions. Whether intentionally or not, such a conceptual reduction of mental disorders to biological dysfunctions may lead psychiatrists to neglect or 'shut out' therapeutic approaches that emphasize cognitive-behavioral, psychodynamic, social, or environmental aspects of the disorder (Schacht and Nathan 1977, 1023; Kirmayer and Young 1999).

On the surface, the assumption that mental disorders stem from biological dysfunctions appears to be confirmed by the fact that biological research has been successful at uncovering disparities between the brains of patients with schizophrenia and those of normal controls. Although no single anomaly is sufficient or necessary for schizophrenia – that is, there are no biological differences that all and only persons with schizophrenia share (Heinrichs 2001, 249) – there are nonetheless promising results that suggest that, in at least some cases, some of the diverse symptoms of schizophrenia, such as delusions, hallucinations, disorganized speech or behavior, affective flattening or avolition (American Psychiatric Association 2000, 312), may be associated with genetic and neurobiological differences. Though there may be no unique and reliable biological indicator of schizophrenia, the diverse evidence of biological discrepancies cannot be ignored.

However, one cannot infer validly from the fact that schizophrenia is associated with a biological *difference*, that this difference represents a biological *dysfunction*. There are three main reasons for exercising caution in this inference. First, just because something is different or unusual, that does not mean it is dysfunctional (e.g., Boorse 1977, 546). Left-handedness is statistically unusual but is probably not the result of a dysfunction, even if it has a distinct biological cause. Moreover, even if a biological condition is maladaptive, unfortunate, or inopportune, this does not mean that it is dysfunctional. It is unfortunate that childbirth is often painful but that does

not mean that normal childbirth is caused by a dysfunction of the female reproductive system (ibid., 547). By similar reasoning, it is often maladaptive for a person to suffer hallucinations or delusions, but that does not mean that the production of hallucinations is the result of some dysfunction. That represents a further claim for which independent empirical evidence must be adduced.

Second, as Schwartz (2007, 383) points out, there are conventional elements involved in 'drawing a line' between the lower range of normal performance for a given organ, on the one hand, and dysfunction, on the other. For example, how and where one 'draws the line' between the lower end of normal thyroid production, and hypothyroidism, depends partly on one's assessment of how significant the negative consequences are of low thyroid production for important aspects of functioning. This is a judgement that leaves room for professional disagreement. That implies that something considered 'dysfunctional' in one scientific or medical context may be considered 'non-dysfunctional' in another.

Third, even something that seems 'dysfunctional' on the surface may have adaptive or functional significance (Richters and Cicchetti 1993, 15; Richters and Hinshaw 1999, 442-443). For example, the diagnostic criteria for conduct disorder (APA 2000, 93-99) include aggression, deceitfulness, and rule-violation. (Conduct disorder is primarily diagnosed of children or adolescents; antisocial personality disorder is reserved for adults, but many of the diagnostic criteria are shared by both categories.) As Richters and Cicchetti (1993) point out, if a child or adolescent expresses antisocial behavior patterns, such as anger, defiance, and oppositionality, this may suggest the presence of a dysfunction, but it may also implicate a developmental context in which those behaviors and attitudes were differentially reinforced, such as a war zone. Relative to the latter context, the behaviors in question should be considered 'functional' given the background in which they were formed.

Similar examples can be found on the neurobiological level. For example, if a person loses sight in one eye at an early age owing to an accident or trauma, the brain will compensate by retaining more neuronal connections between the functioning eye and the visual cortex (e.g., Kaas 1991). This has the consequence of bestowing greater powers of visual discrimination

upon the functioning eye. Anatomically, such brain structures appear highly unusual, yet they have obvious functional and adaptive significance for the individual, given that individual's unfortunate life circumstances. By analogy, it may be that some of the neurobiological differences associated with schizophrenia have important adaptive or functional significance, given a context of unusual or adverse life experiences. For these reasons, one should remain cautious in concluding that mental disorders such as schizophrenia necessarily stem from biological dysfunctions.

It is appropriate to provide some clarification of the relevant sense of 'dysfunction' at issue in this paper. There are at least three important senses in which a trait is said to 'dysfunction.' In one sense, 'dysfunction' is construed as a type of 'internal breakdown,' 'defect,' or deviation from optimal, typical, or evolved 'design.' For example, multiple sclerosis involves damage to the myelin sheath and prevents myelin from carrying out its function of conducting impulses. This represents a dysfunction of the myelin, regardless of whether multiple sclerosis is an autoimmune disorder, pathogen mediated, or influenced by genes. Similarly, Duchenne muscular dystrophy is due to a mutation that prevents the dystrophin gene from carrying out its function of producing the dystrophin protein. As a consequence, the dystrophin gene is 'dysfunctional' because it cannot perform its function due to a structural alteration. This is the type of dysfunction typically sought by biologically-oriented psychiatric researchers. It is also the sense that will be at issue in this paper. When it is questioned whether schizophrenia stems from a 'dysfunction,' it is dysfunction in this sense of 'internal breakdown' that is implied.

In another sense of the term 'dysfunction,' something can fail to function because it has been placed in an 'uncooperative environment,' that is, an environment that falls outside of its normal or historical range, as a consequence of which the resources necessary for its proper functioning are not present.[1] In a dark room one's eyes are unable to carry out their function of seeing, even though they are not dysfunctional in the sense of an 'inter-

[1] The distinction between these two different senses of dysfunction is developed in Dretske (1986) and Neander (1995), and will be discussed in more detail in Section 2.2.

nal breakdown.' If a person is submerged in water, his or her lungs cannot perform their function of distributing oxygen throughout the body. At least initially (a short time after submergence) the lungs are *not* dysfunctional in the sense of an internal breakdown but are simply unable to carry out their function due to an abnormal environment. (Of course, extended submergence will result in the inhalation of water, which causes lung injury, which is a type of 'internal breakdown.') The distinction between these two senses will be developed in Section 2.2. However, in the following the term 'dysfunction' will be reserved for the first sense (i.e., internal breakdown). The second sense of 'dysfunction' will be referred to instead as the 'inability to function owing to an abnormal environment.'

There is a third sense of 'dysfunction' relevant to psychiatry according to which an individual's behavior or dispositions are 'dysfunctional' because they give rise to maladaptive or harmful consequences, either for the individual or his or her social group. For example, the characteristic symptoms of antisocial personality disorder are clearly dysfunctional in this sense because they typically have harmful consequences for the individual such as the inability to hold down a job or maintain long-term friendships. However, the fact that antisocial personality disorder is dysfunctional in this latter sense (or 'socially dysfunctional') does not imply that it represents a dysfunction in the sense of an 'internal breakdown.' It may be that in some individuals, the characteristic behaviors associated with antisocial personality disorder represent an adaptive response to an unusually hostile environment, in which case they would *not* be dysfunctional in the sense of an 'internal breakdown.' This final sense of dysfunction as 'social dysfunction' will not be used in this paper. It is sufficient to point out that a pattern of action may be socially dysfunctional without stemming from a dysfunction in the sense of an internal breakdown. Political activism can be dysfunctional in the sense of 'socially dysfunctional' even if it does not stem from an internal breakdown (e.g., a neurobiological or genetic dysfunction; see Spitzer and Endicott 1978, 28).

When it is questioned, then, whether schizophrenia stems from a dysfunction, what is in question is whether it is 'dysfunctional' in the first sense, namely, that it represents some sort of 'internal breakdown.' *Clearly*, schizophrenia is usually dysfunctional in the sense of socially dysfunctional. It

is possible that schizophrenia is dysfunctional in the second sense, namely, that it involves an adaptation to an unusual environment as a consequence of which certain functions associated with the normal environment cannot be performed.

The following is divided into four main sections. Section 2 examines recent philosophical work on the concept of biological function and introduces two distinctions that are useful for interpreting empirical models of schizophrenia. Section 3 describes one particular model of schizophrenia which holds that schizophrenia is the result of synaptic 'pruning' mechanisms that affect the neurotransmitter glutamate. It argues that current evidence does not warrant the claim that the glutamate system in schizophrenia is dysfunctional, and argues that the evidence could, with equal facility, be taken to suggest that it is functioning adaptively in the face of adverse life events. The fact that the evidence is ambivalent between these two readings (*dysfunction* versus *adaptive function*) implies that schizophrenia researchers should be much more cautious in using the 'dysfunction' label than they currently are. The final section (Section 4) develops implications for both the treatment and public perception of schizophrenia.

2. Biological Functions and Dysfunctions

An enormous amount of philosophical work on the concept of biological function and dysfunction has been published over the last 40 years (see Garson 2008 for a comprehensive survey). The majority of philosophers participating in the debate can be divided into two main camps – etiological theorists and consequentialist theorists. According to the etiological (or 'backwards-looking') approach to functions, a biological part or process has a 'function' because of the historical process that explains its current existence or form. According to the consequentialist (or 'forward-looking') approach to functions, a biological part or process has a function because of one of the effects or consequences it typically produces, rather than its history.

To take a simple example, according to one etiological approach called the 'selected effects' theory, the human heart has the function of circulating blood because historically, circulating blood is what caused hearts to be

selected for by natural selection and therefore it explains why humans have hearts today (e.g., Neander 1983; 1991; Millikan 1984; 1989; Sober 1984, 208; Brandon 1990, 184-189; Griffiths 1993; Godfrey-Smith 1994; Mitchell 1995; Allen and Bekoff 1995; Schwartz 1999). According to one consequentialist approach, the heart has the function of circulating blood because circulating blood contributes to the fitness of the organism that possesses it, regardless of its evolutionary history (e.g., Ruse 1971; Boorse 1976; Bigelow and Pargetter 1987; Horan 1989; Wouters 2003).

For the purpose of this article, a version of the etiological theory of functions will be adopted. According to this theory, the function of a biological part or process consists in that activity which historically led to its *differential reproduction or differential retention within a biological system*. Roughly speaking, the function of a biological entity or process consists in the activity that it was 'selected for.' However, the expansive sense of 'selection' embedded in this definition will be explicated in Section 2.1. The reason that an *etiological* theory of function rather than a consequentialist one is used is that it lends itself easily to the construction of a well-defined concept of dysfunction, while it remains controversial whether consequentialist theories can be used to define 'dysfunction' (e.g., Millikan 1989, 294; Neander 1991, 181). However, a similar conclusion (that schizophrenia cannot be reduced to a biological dysfunction) could be drawn even under a consequentialist theory of function (see Section 2.2). The conclusion regarding schizophrenia, then, does not rely exclusively on accepting one or another position in the controversial function debate.

Two important points about this etiological theory of function should be addressed before defining a corresponding notion of 'dysfunction.' The first concerns the expansive sense of 'selection' appealed to in the definition above (Section 2.1). The second concerns the distinction between dysfunction and the inability to function owing to an abnormal environment (Section 2.2).

2.1. A Generalized Version of the Selected Effects Theory

Many proponents and detractors of the selected effects theory have stated that according to that theory, natural selection operating at the level of the individual organism, and over an evolutionary time scale, is the only pro-

cess relevant for the ascription of biological functions (e.g., Sober 1984, 208; Brandon 1990, 186; Neander 1991, 174; Allen and Bekoff 1995, 612; Walsh and Ariew 1996, 497; Wouters 2003, 649-652; Lewens 2007, 533). As a consequence, it is widely assumed that the selected effects theory cannot ascribe functions in any direct manner to evolutionarily novel traits. The problem with this restrictive notion of 'selection' is that in order to determine whether or not a trait *has* a function, and *which* function it has, one would have to possess extensive knowledge about its evolutionary history. In particular, one would have to know *that* the trait was selected for by natural selection and *what* it was selected for.

Unfortunately, the precise evolutionary histories of many of the psychological (and even biological) traits that psychiatrists are interested in are shrouded in mystery (e.g., Lewontin 1998). Despite the expansive claims of movements such as evolutionary psychology or evolutionary psychiatry (e.g., Buss 1999; Nesse 1999; Stevens and Price 2000), the evolutionary history of psychological traits such as sadness, anxiety, aggression, and so on, are not transparent to us. If functions are determined exclusively by evolutionary history, then many function ascriptions will appear, at best, unscientific, and at worst, as reflections of current social and ideological biases rather than biological reality (e.g., Gould and Lewontin 1979). This point has often been raised in the psychiatric context specifically against Wakefield's (1992, 1993, 1999) attempt to identify the function of a trait with the activity that it was selected for by natural selection (see McNally 1994, 205; Lilienfeld and Marino 1995, 413; Sadler and Agich 1995, 226-7; Sadler 1999, 435; Kirmayer and Young 1999, 449; Woolfolk 1999, 660; Bolton 2001, 198-9; Murphy and Woolfolk 2001, 245; see Buss et al. 2002 for a response).

Fortunately, there are other types of 'selection processes' in the natural world in addition to natural selection (Darden and Cain 1989; Cziko 1995; Hull et al. 2001). There are three in particular that are worth mentioning: *neural* selection processes, antibody selection processes, and selection processes underlying some types of learning such as operant conditioning. These can satisfy the selected effects theory of functions and they operate over a much shorter time-frame (Wimsatt 1972, 15; Godfrey-Smith 1992; 2009; Millikan 1984, 28; Papineau 1987, 66; 1993, 45; 1994). As a

consequence, it is not always necessary to explore or even speculate about the ancient evolutionary history of an organism in order to determine that certain parts or processes within it have 'functions' in this broader sense – a point often leveraged against the selected effects theory of function (e.g., Amundson and Lauder 1994, 356-61; Schlosser 1998, 323-4; Wouters 2005, 144). The etiological theory of functions allows functions to emerge over the lifetime of an individual. This move substantially broadens the range of evidence that would be relevant to show that a given trait possesses a function. These three types of selection processes will be briefly described.

First, there are *neural selection* processes that operate over an individual's lifetime (Changeux and Danchin 1976; Edelman 1987). Along with other neurological processes, neural selection is responsible for sculpting the mature pattern of synapses in the brain. During early infancy, the human brain produces a 'hyperabundance' of neural connections. That is, it produces many more neurons and synapses than it will retain. From childhood through adolescence, many of these connections are removed or eliminated. This is also referred to as 'synaptic pruning.' The specific pattern of connections in the mature brain is largely due to the elimination of existing synapses, although new synapses are continuously formed as well (Huttenlocher 1979; Rakic et al. 1986).

The crucial point is that *which* neurons are retained, and which are eliminated, is often due to a 'competition' between them. Neurons, like organisms, need external resources for growth and repair. Some of these resources are called 'trophic factors' and they depend on a neuron's ability to synapse onto other neurons. That is, when a neuron *A* synapses onto a neuron *B*, some of the nutritive resources that *A* needs to sustain its form come from neuron *B*. When many different neurons form synapses with the same target neuron, they may compete for the trophic factors produced by that target neuron. Some of these neurons may be better positioned than others to exploit this trophic factor, and as a result, they tend to be retained as others are eliminated (see Figure 1). Neural selection has been shown to play a role in the formation of diverse neural structures such as the neuromuscular junction, ocular dominance columns in the visual cortex, brain regions underlying filial imprinting, and the structure of the olfactory system in mammals (see Wong and Lichtman 2002 for a review).

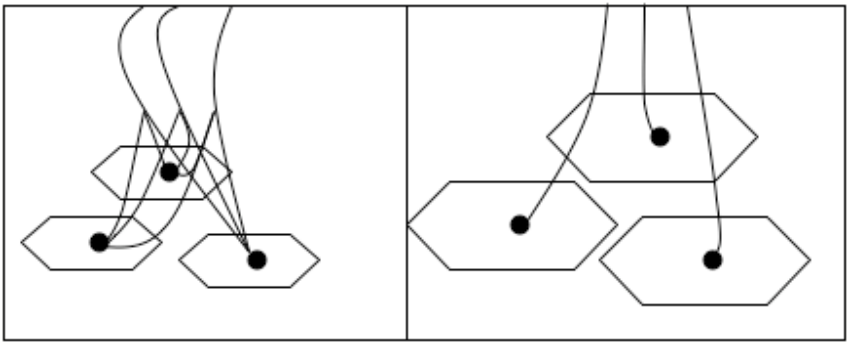

Fig. 1. Innervation of skeletal muscle of newborn rats. The first panel depicts the multiple innervation of muscle fibers by motor neurons; the second panel depicts the one-to-one pattern of connections that emerges by two weeks after birth. Redrawn from Purves and Lichtman (1980, 155).

Selectionist models are also used to explain the development of the immune system. According to the clonal theory of antibody production, certain antibodies are reproduced over others upon exposure to the corresponding antigen (Burnet 1959; see Rajewsky 1996 for a recent review). Finally, some forms of learning, such as operant conditioning, can be modeled as selection processes. In operant conditioning, certain behavioral dispositions are reinforced over others by virtue of their performance on a common task. (McDowell 2009 gives a recent defense of what he calls 'behavioral Darwinism' and provides a formal comparison with 'neural Darwinism.')

All of these phenomena – natural selection, neural selection, antibody production, and operant conditioning – exhibit a similar basic process. Certain structures are reproduced over other structures, or retained over other structures, by virtue of their activity. This basic process establishes what Wright (1976, 113) called a 'consequence etiology,' in which certain effects produced by a structure explain the continued persistence of that structure. Moreover, such structures are selected for, that is, *differentially* reproduced or retained over other structures. As a result, they should be taken to satisfy the selected effects theory of function.

This generalization of the etiological theory has a consequence, however,

that is crucial for assessing whether a given trait is functional or dysfunctional: *the fact that a given biological trait is structurally unusual, or that a given psychological trait is maladaptive or inappropriate, does not imply that it is 'dysfunctional.'* An example from neuroscience can illustrate the point.

In the 1960s, neuroscientists David Hubel and Torsten Wiesel famously carried out single-cell observations on the mammalian visual cortex (Wiesel and Hubel 1963; Hubel and Wiesel 1965). In some of these experiments (known as 'monocular occlusion' experiments) the scientists deprived newborn kittens of visual stimulation in one eye for the first few months of life, and recorded electrical activity from single cells in the visual cortex. Two notable results emerged; one was expected and the other was unexpected. The expected result was the almost complete absence of neural connections between the visual cortex and the deprived eye as reflected in the impoverished width of the ocular dominance columns associated with that eye. The unexpected result was that the vast majority of visual neurons responded exclusively to stimulation of the non-deprived eye as shown by a corresponding thickness in the ocular dominance columns for that eye (also see Rakic 1976; Hubel et al. 1977). Effectively, the visual cortex had reorganized itself in such a way as to enhance the discriminatory power of the functioning eye, and accrued new functions in the process.

Crucially, the unusual thickness of the ocular dominance columns for the functioning eye is the result of a neural selection process. About 80% of the neurons of a kitten's visual cortex are 'binocularly-driven,' that is, they are responsive to light coming in from either eye. However, when a newborn kitten is deprived of vision in a single eye for the first several months of life, most of the neurons in its visual cortex become 'monocularly-driven,' that is, responsive only to stimulation of the functioning eye. Unlike kittens that have undergone monocular deprivation, however, kittens that have been exclusively dark-reared for the first several months of life appear to retain the same degree of binocularity as normal kittens. This implies that the results of the monocular-deprivation experiments cannot be explained by the assumption that connections from the deprived eye degenerate as a function of disuse. Rather, it implies that there exists some active 'competition' between the neural connections from the deprived eye and the non-de-

prived eye (Wiesel and Hubel 1963, 1015) – that is, the loss of connections from one eye is a consequence of the activation of the other eye.

Now for a thought-experiment: suppose a neuroscientist were to encounter tissue samples from the kitten's visual cortex but he or she knew nothing about the life experience of the kitten. He or she would probably be inclined to think that the gross neurostructural anomalies in the visual cortex (such as the unusual width of ocular dominance columns) represent a dysfunction. The truth is that the visual cortex is not dysfunctional, but can be said to be functioning adaptively in the face of the kitten's adverse experience. This is because neural selection processes were responsible for generating novel functions in response to the unusual formative environment.[2] This example illustrates the point that structural differences alone do not provide sufficient evidence to infer the existence of a dysfunction. A biological trait may be structurally unusual precisely *because* it has been adapted to an unusual environment, and not because of some 'internal breakdown' or 'defect.'

2.2. Dysfunction and Inability to Function Owing to Abnormal Environment

Secondly, there is an important distinction to be drawn between the case in which a biological part is *dysfunctional*, and the case in which it is *unable to perform its function owing to an abnormal environment* (e.g., Dretske 1986, 32; Neander 1995, 119-120). For example, if one binds a person's legs with rope, the legs will be unable to perform their natural function of walking – but that does not mean they are dysfunctional. Rather, they are simply prevented from performing their function by unusual environmental circumstances. More generally, for any given biological entity, *X*, and any function, *F*, the functional status of *X* with respect to F does not

[2] Of course, it may be that the unusual cortical structures in the case of monocular occlusion have functions because the visual cortex was selected for by natural selection to possess the sort of plasticity that it exhibits in this situation; this would be along the lines of Millikan's distinction between 'direct' and 'derived' proper functions (e.g., Millikan 1984, 41-42; 1989, 288). However, the point of the above discussion is that this hypothesis, or *any* hypothesis regarding the evolutionary history of the visual system, is not *necessary* for determining that the unusual structure in question has a function.

merely fall under one of two mutually exclusive categories – functional or dysfunctional – but rather, one of three different categories: *X* has the function *F* and is capable of performing this function (functioning properly); *X* has the function *F* but is unable to perform *F* due to an abnormal environment; *X* has the function F but is unable to perform *F* where this inability is not due to an abnormal environment.

The importance of this distinction can be illustrated by a neurobiological example relevant to psychiatry. This example also shows the need for caution in inferring that a particular biological system is 'dysfunctional.' Until recently, most biologically-oriented psychiatrists believed that schizophrenia – or at least some of its so-called 'positive' symptoms such as hallucinations or delusions (as opposed to 'negative' symptoms such as avolition or alogia) – is caused by an overproduction of the neurotransmitter dopamine in the ventral tegmental area (VTA) of the midbrain. Dopamine-carrying neurons in this region affect both the limbic system (a brain region implicated in the regulation of emotion and motivation) and the prefrontal cortex (implicated in the temporal organization of behavior, motivation, and attention). Consequently, unusual dopamine production in the VTA can profoundly affect emotion and cognition.

The view that schizophrenia is primarily caused by an overproduction of dopamine is called the 'dopamine hypothesis' of schizophrenia (Carlsson 1974; Pliszka 2003). Its development helped to promote a largely successful research paradigm that sought the origin of certain mental disorders in abnormal neurotransmitter production. It also led many psychiatrists to accept the rather simplistic conclusion that schizophrenia stems from a dopamine 'dysfunction.'

However, more recently psychiatrists have begun to abandon this model and to focus attention on the role of other neurotransmitters in schizophrenia, including the neurotransmitter glutamate (Grace 2000; Carlsson 2001). Glutamate-carrying neurons in the prefrontal cortex release glutamate onto dopamine neurons in the VTA and therefore affect dopaminergic behavior. According to one theory, the root neurobiological cause of schizophrenia is the *under*production of the transmitter glutamate ('glutamate hypofunction'). Heightened dopamine production would merely represent a byproduct of the glutamate hypofunction. In this case, while one might say

that the glutamate system is 'dysfunctional,' the dopamine system is not 'dysfunctional' but rather 'unable to function normally due to an abnormal (glutamatergic) environment.' This is because, if the glutamate system were restored to normal functioning, the dopamine system would resume its normal functioning as well. Thagard (2003, 244) uses the term 'internal' and 'external' malfunction to describe the distinction between the primary locus of malfunctioning and the secondary effects of that malfunction. Here the term 'dysfunction' is used narrowly in the sense of an 'internal malfunction.'

The failure to attend to this important distinction gave rise to the unwarranted inference that because of unusual levels of dopamine activity in schizophrenia, there must be a 'dysfunction inside' the dopamine system. Psychiatric researchers did not consider the alternate possibility that unusual levels of dopamine represent a byproduct of unusually low levels of glutamate. At least in this narrow sense of the term (i.e., 'internal malfunction') one should not say that the dopamine system is 'dysfunctional' but rather than it is unable to function normally due to an abnormal neurochemical environment.

The inference that the dopamine system in schizophrenia was 'dysfunctional' went hand-in-hand with aggressive pharmaceutical intervention targeting the dopamine system (the so-called 'typical antipsychotics'). Such interventions often resulted in disabling extrapyramidal effects, most notoriously the Parkinsonian-like dyskinesias. A newer generation of antipsychotics (the 'atypical' antipsychotics) target a broader array of neurotransmitters and are associated with fewer extrapyramidal effects (e.g., Kapur and Seeman 2001). Consequently, inferences regarding the locus of 'dysfunction' in the psychiatric context have significant theoretical as well as practical bearing.[3] This is not to say that an inadequate theory of function is what *caused* researchers to accept the dopamine hypothesis. However, it may have contributed to researchers' failure to explore other alternatives, including the possibility that dopamine overproduction was merely a byproduct of

[3] Buller (1997), for example, proposes to define 'dysfunction' in terms of the target of intervention or repair, thus wedding the definition of 'dysfunction' to the interventions necessary to ameliorate it.

a dysfunction in some other part of the brain.

Equipped with these two points, a concept of biological *dysfunction* can be straightforwardly defined. To say of an individual entity, *X*, that it is dysfunctional with respect to some activity, *F*, means that:

(i) the function of *X* is *F*;
(ii) *X* is not able to perform *F*; and
(iii) if X is not in the normal environment for its functioning, then if *X* were in the normal environment for its functioning, *X* would not be able to perform *F*.

Condition (iii) ensures that *X*'s inability to perform *F* is not (merely) due to an abnormal environment.

Two facets of this definition deserve mention before the example of schizophrenia is developed in more detail. First, this definition rests crucially on the notion of a 'normal environment for an entity's functioning.' From an etiological (historical) perspective, a 'normal environment for an entity's functioning' can be taken to refer to the range of environments within which the entity's progenitors performed the activity that currently constitutes its function, and in which those performances contributed to the differential persistence or differential reproduction of that entity or type of entity. (Roughly, this is the range of environments to which the trait has been 'adapted.') The view that the function of an entity is relative to a 'normal environment' is fairly standard in philosophical discussions of etiological function (e.g., Millikan 1984, 33-4), even if it is left implicit. In fact, some notion of a 'historically normal environment' has also been invoked in the context of consequentialist definitions of function, so it alone does not distinguish between the two theories of function (e.g., Boorse 2002, 99).

Secondly, there are two different senses in which a trait can fall outside of its 'normal environment,' a *synchronic* sense and a *diachronic* sense. The first, synchronic, sense concerns the way in which the *current* environment of the trait may fall outside of the 'normal' range. This would be exhibited if a person's legs were bound by rope or a person were submerged underwater. The second, diachronic, sense concerns the way in which the trait may represent an adaptation to an abnormal *past* environment that the individual

was exposed to. An obvious example would be the use of camouflage in changing environments. A chameleon may adapt to changing environments by changing color to match its background (e.g., turning green to match a green background). However, its ability to change color is fairly limited and not as rapid as is commonly believed. Consequently, if its environment changes rapidly, that adaptation will no longer serve its function and the chameleon will be vulnerable to predation. However, the green skin color is not by that token 'dysfunctional' in the sense of an internal breakdown. Rather, it represents the proper functioning of the pigment rearranging mechanism in a changing environment. Similarly, the unusual width of ocular dominance columns in the kitten's visual cortex is not dysfunctional, but rather represents an adaptation to an unusual formative environment.

Naturally, not all sorts of environmentally-induced changes represent 'adaptations.' Developing cancer from exposure to environmental carcinogens would represent a dysfunction even though it is environmentally caused. If a person's arm is restrained throughout youth and as a consequence he or she loses the use of that arm, this would certainly represent a dysfunction even though it was environmentally caused.[4] However (as will be emphasized below in Section 3) it is important to distinguish environmentally-induced biological changes that represent adaptations and those that represent dysfunctions – a distinction which fails to be made in much biological research in psychiatry.

What this section has shown is that, regardless of the specific theory of function one accepts, one should be cautious in drawing the conclusion that schizophrenia stems from a biological dysfunction. As long as one's theory of function allows one to draw the distinction between the case in which something is *dysfunctional*, and the case in which it is *unable to function normally owing to an abnormal environment*, then one should exercise extreme caution in inferring that a given neurobiological structure is dysfunctional merely because of structural differences.

[4] I am grateful to an anonymous reviewer for suggesting that illustration.

3. Schizophrenia and the Glutamate System

This section will examine a specific neurochemical hypothesis for schizophrenia called the glutamate hypothesis. According to this view, some of the 'positive' symptoms associated with schizophrenia such as hallucinations or delusions are caused by the glutamate system. After introducing the hypothesis, it will present the possibility that the supposed glutamate abnormality may result from an adaptive response on the part of the brain to unusual or adverse formative experiences, including emotional experiences. Thus, this section provides a plausible scenario in which, despite the neurobiological differences associated with schizophrenia, nothing 'within' the brain is dysfunctional at all. The fact that, as will be shown, the data is ambivalent between these two possibilities (dysfunction *versus* adaptation to unusual environment) implies that researchers should be much more cautious than they currently are in uncritically assuming that schizophrenia must stem from an inner 'dysfunction' or 'breakdown.'

As noted in the previous section, many psychiatrists have begun to emphasize the role of the glutamate system in schizophrenia. Several pieces of evidence implicate the underproduction of glutamate in the prefrontal cortex. One piece of evidence is that psychostimulants such as PCP inhibit the glutamate receptor and produce symptoms analogous to schizophrenia (Olney et al. 1999). Secondly, functional imaging studies have implicated decreased prefrontal activity in schizophrenia, which would indicate a relative decrease in glutamate activity in that region (Carlsson and Carlsson 1990). Thirdly, some preliminary reports suggest that administration of glycine, a glutamate receptor agonist, alleviates schizophrenic symptoms (Meltzer and Deutch 1999).

Nonetheless, it would be premature to conclude that hypofunction in the glutamate system represents a dysfunction. As an alternative, it may be that changes in the glutamate system represent a functional, adaptive response to unusual or adverse formative experiences. This latter possibility is rendered plausible by considering the role of neural selection processes in shaping the mature form of the glutamate system, and the dependence of those processes on the individual's formative environment.

The glutamate neurons that are held to be responsible for schizophrenia largely reside in the prefrontal cortex of the brain. These neurons release glutamate onto dopamine neurons in the VTA, which explains their important effect the normal functioning of the dopamine system (Carlsson and Carlsson 1990; Grace 1991). Crucially, the shape, number, and connectivity of these glutamate-carrying neurons are, at least in part, formed by neural selection processes (as described in Section 2.1). In other words, in early neurological development there seems to be a 'hyperabundance' of connections between glutamate neurons in the prefrontal cortex; over the course of the individual's cognitive and physical development, some of these connections are retained, and others eliminated. The mature form of the glutamate system is partly the result of the synaptic 'pruning' of unnecessary or ineffective connections (Keshavan et al. 1994; Lewis 1997; McGlashan and Hoffman 2000).

That the mature form of the glutamate system is shaped by synaptic pruning has led some theorists to speculate that an unusually long or 'excessive' period of synaptic pruning may lead to a reduction in the number of connections between glutamate neurons, and that this reduced connectivity may result in the glutamate hypofunction implicated in schizophrenia (McGlashan and Hoffman 2000; Etienne and Baudry 1990). (See Figure 2.)

The hypothesis that glutamate hypofunction is caused by an unusually long or intensive window of synaptic pruning leads to the following question: what might be responsible for the unusual duration or intensity of synaptic pruning? As it turns out, the nature and duration of the synaptic pruning process may depend on the individual's formative experiences including emotional experiences (see Figure 3).

Evidence for this hypothesis is suggested by reports that the extent of

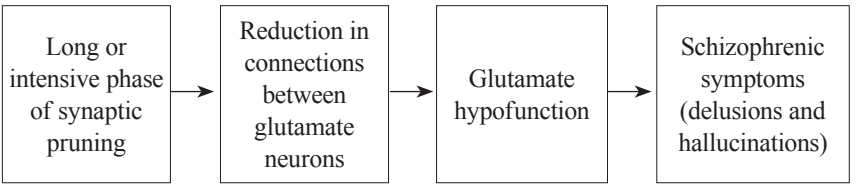

Fig 2. Proposed relation between synaptic pruning and schizophrenic symptoms.

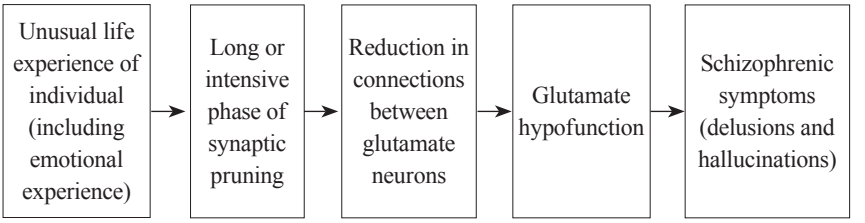

Fig. 3. Proposed relation between unusual life circumstances and schizophrenic symptoms.

neural selection ('pruning') in the forebrain may be related to *emotional* experience (Bock and Braun 1998). In newborn chicks, the extent of neural pruning in the neostriatum was correlated with the degree of experience with a mother surrogate. Experience with the mother surrogate both initiated and shaped the course of synaptic pruning in chicks. Is it overly speculative to suggest, as the authors of this study do, that adverse emotional experience in humans may also result in an unusual degree of synaptic pruning (Ibid., 25)?

Some psychiatric researchers have acknowledged the possibility that synaptic pruning is controlled in part by the individual's life experiences, and have even suggested that the environmental dependence of synaptic pruning provides a way to model the interaction of 'biological' and 'environmental' factors in the etiology of schizophrenia. As Keshavan et al. (1994) note, one strength of the pruning model of schizophrenia is that the environmental-dependence of synaptic pruning would "allow for the integration of psychosocial factors into this pathophysiological model" (Ibid., 257). Moreover, they argue,

> "In view of the possibility that experience may influence selective survival of certain synapses, it is conceivable that genetic abnormalities of programmed synaptic pruning processes and adverse life experiences in early life could interact to result in pathological brain maturation and consequently the schizophrenic diathesis" (Ibid; also see Feinberg 1982/1983).

If characteristic symptoms of schizophrenia are partly the result of an unusual or adverse formative environment, this raises the possibility that the neurobiological differences underlying schizophrenia represent an adaptive and functional response *to* that unusual environment. If this is so, it would be inappropriate to say that schizophrenia stems from a biological – or even an internal – dysfunction at all, despite the painful or maladaptive consequences that the schizophrenic symptoms may have in the life of the individual. Rather, the 'abnormality' in question would be associated with the formative external environment and not with the *internal milieu* of the person with schizophrenia. The development of the visual cortex under monocular occlusion constitutes an obvious analogy to the situation. Since the evidence is ambivalent between these two possibilities (*dysfunction versus adaptation to an unusual circumstance*) one should exercise caution in inferring that schizophrenia necessarily stems from an inner dysfunction.

One potential objection that may be raised here is this: all that the example of synaptic pruning has shown is that *biological differences underlying schizophrenia may be caused, in part, by the environment*. That fact would not be terribly surprising because other disorders have also been shown to have an environmental component (e.g., Caspi et al. 2003). In particular, it has not been shown why these differences should be seen as adaptive or functional. The mere fact that a neurobiological change is environmentally caused does not imply that it is functional or adaptive. For example, inhaling lighter fluid can cause massive dysfunction in neurons throughout the prefrontal cortex. There is nothing functional or adaptive about that response.

It is true that the brain may respond in many different ways to environmental insults. On the one hand, the inhalation of lighter fluid may cause massive cellular dysfunction. On the other hand, in addition to the cellular dysfunction, there may also be secondary responses that are functional and adaptive, and that contribute to healing. For example, the inhalation of lighter fluid will also cause blood to rush to affected regions to bring nutrients to vulnerable neurons. Environmental shocks or traumas may cause both dysfunctional as well as functional responses. The problem is that it is often difficult to tell whether a given part of the brain is dysfunctional or whether it is responding in an adaptive and functional manner to changing

circumstances. After all, the *modus operandi* of the brain is to reorganize itself in response to novel environmental demands. As a consequence, what the example regarding synaptic pruning shows is that one must exhibit extreme caution in making the inference that a neurobiological difference represents a dysfunction. This is particularly so when the presence or the absence of the change appears to be systematically dependent on the life history of the individual. Given the environmental-dependence of schizophrenia, much more research would need to be conducted before embracing the conclusion that it represents an inner dysfunction.

To reiterate, the purpose of this section is not to present evidence that schizophrenia is functional and adaptive rather than dysfunctional. The purpose is to show that given a plausible theory of function, the evidence for a 'dysfunction' is highly ambivalent between the claim that schizophrenia represents a dysfunction and the claim that it represents an adaptive response to an unusual environment. The fact that schizophrenia seems to exhibit a strong environmental-dependence, and that the brain is constantly reorganizing itself to adapt to environmental challenges, shows that this is a plausible alternative to the 'dysfunction' theory.

A second objection would be based upon the supposed genetic components of schizophrenia. According to this objection, schizophrenia has been shown to have a genetic component, and the existence of this genetic component reveals that it stems from an internal dysfunction. However, there are two problems with this objection. The first is that evidence for a genetic basis for schizophrenia is highly ambivalent. Although many believe it to be influenced genetically (Moises and Gottesman 2001; Tsuang 2000), it certainly does not follow a classic Mendelian pattern of inheritance, and attempts to localize specific genes have not been successfully replicated (Riley and McGuffin 2000; Torrey and Yolken 2000; see Sarkar 1998 for general problems with attempts to 'reduce' complex psychological or behavioral traits to genes). But a second problem is more significant. Even if schizophrenia has a genetic component, that does not imply that it stems from a dysfunction. After all, many unusual or statistically rare phenotypes have a genetic component but are not dysfunctional, such as red hair or green eyes (e.g., Lloyd 1998). In order to determine that schizophrenia stems from a genetic dysfunction one would have to ascertain, first, the function

of the relevant gene, and second, that the variant associated with schizophrenia prevents that function from being carried out. For example, if there is a sequence of DNA that has the *function* of regulating the connectivity of glutamate neurons in the prefrontal cortex, and if schizophrenia stems from a mutation that prevents this function from being executed, then it would be true to say that schizophrenia stems from a dysfunction. However, none of this could be inferred without further evidence.

The possibility that changes to the glutamate system in schizophrenia may have functional or adaptive significance is not proposed here as an ascertained fact. Rather, it is merely suggested as a plausible hypothesis given what is known about common neurobiological processes – one that could be progressively confirmed, or disconfirmed, in the face of future evidence. However, to the extent that this hypothesis is plausible, then one cannot infer merely from the presence of neurobiological differences associated with schizophrenia that schizophrenia stems from a biological 'dysfunction.' Unfortunately, that is precisely the inference that psychiatrists and neuroscientists routinely make.

The pertinent analogy here is to the unusual structure of the visual cortex of kittens raised in conditions of monocular occlusion. Of course, the difference between the cases is that in the latter case, the functional and adaptive value of the unusual structure is *known*: it maximizes the kitten's power of visual discrimination. The possible functional or adaptive role of glutamate differences underlying schizophrenia is unknown, although such an adaptive role is not inconceivable. For example, one theory of schizophrenia that was prominent in the 1960s was the 'double-bind' theory associated with the work of Gregory Bateson and colleagues (e.g., Bateson et al. 1956), according to which schizophrenic symptoms such as delusions and hallucinations, catatonia, and disorganized thought can be understood as intelligible responses to conflicting demands that are imposed upon a person (typically by the family) each of which is associated with punishment and which jointly admit of no satisfactory resolution. Delusion, in this view, represents an attempt to 'escape' these conflicting demands. Of course, this paper is *not* endorsing Bateson's 'double-bind' theory. The point, however, is that the supposition that symptoms associated with schizophrenia have adaptive significance is not beyond the realm of plausibility.

4. Implications for Research and Treatment

One might argue that this thesis – that one should be cautious in concluding that schizophrenia stems from a biological dysfunction – is relatively trivial. Who cares if mental disorders do not stem from 'biological dysfunctions,' according to some philosophical definition of 'function'? After all, psychiatrists have found evidence of important and substantial biological differences between the brains of people who do, and do not, have schizophrenia. Secondly, it is agreed that schizophrenia is dysfunctional in the sense of 'socially dysfunctional.' Furthermore, schizophrenia, whatever its basis, can be a horrifying condition – both for the person so afflicted as well as that person's friends and family – one that hopefully will someday be eradicated by the advent of pharmacological and other forms of treatment. It is still a great victory for biological psychiatry that schizophrenia, and other severe mental disorders, can safely be said to stem from biological 'abnormalities,' or to represent 'unfortunate biological conditions,' and that many can be treated pharmacologically. So, one might argue, why should it matter whether or not schizophrenia can be said to stem from a 'biological dysfunction'?

The reason it matters is that the language of 'dysfunction' in psychiatry is powerful and significant. Whether or not the brain can be said to be 'dysfunctional' in the case of a severe mental disorder has a tremendous bearing on the way that mental disorders are conceptualized in psychiatric practice, as well as perceived among the public. On the surface of it, to say that someone has a mental disorder is often to say that something has gone 'wrong,' as it were, *inside* the person. The idea that nature has in some sense 'erred' in the brain of a person with a mental disorder bears, for many, an unmistakable intuitive appeal. It is only natural, then, to want to 'look inside' the person and find out what 'went wrong.' The language of inner 'dysfunctions,' then, supports individualistic models of psychiatry that look 'inside' the person rather than 'outside' the person to his or her environment. This has the unfortunate consequence of potentially restricting research and medical attention solely to the biological processes implicated in schizophrenia, and to downplay or ignore other relevant factors such as cognitive-

behavioral, social, or environmental ones.

It is, of course, empirically possible that schizophrenia, along with other major mental disorders, will be shown unequivocally to stem from internal dysfunctions. But it is also empirically conceivable, and consistent with current evidence, that it does not stem from an inner dysfunction. The mere fact that the 'dysfunction' label tends to have a restrictive effect on research and treatment norms suggests that psychiatrists and researchers should be more cautious in the use of that label than they currently are.

Suppose, furthermore, that one does not say that mental disorders stem from biological dysfunctions, but rather, one merely states that they have biological 'causes,' or that they stem from 'unusual biological conditions,' or simply that the brains of some people with mental disorders are 'different' from the brains of those without? These statements do not carry the same normative weight because they are not accompanied by the implicit suggestion that anything in the brain has 'gone wrong.' The suggestion that the neurobiology underlying some forms of schizophrenia reveals an 'adaptive response of the brain to an unusual formative environment' may, in fact, encourage researchers to explore the complex interactions between life experience and brain development that may contribute to schizophrenia and other major mental disorders (e.g., Caspi et al. 2003). Taking this perspective to an extreme, one might suggest that the unusual biological formations associated with schizophrenia represent a creative triumph of the human brain to adapt to unusual or adverse events.

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