Plastic Adaptation to Pathology in Psychiatry: Are Patients with Psychiatric Disorders Pathological Experts?

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Abstract
Psychiatric disorders share the same pattern of longitudinal evolution and have courses that tend to be chronic and recurrent. These aspects of chronicity and longitudinal evolution are currently studied under the deficit-oriented neuroprogression framework. Interestingly, considering the plasticity of the brain, it is also necessary to emphasize the bidirectional nature of neuroprogression. We review evidence highlighting alterations of the brain associated with the longitudinal evolution of psychiatric disorders from the framework of neuroplastic adaptation to pathology. This new framework highlights that substantial plasticity and remodeling may occur beyond the classic deficit-oriented neuroprogressive framework, which has been associated with progressive loss of gray matter thickness, decreased brain connectivity, and chronic inflammation. We also integrate the brain economy concept in the neuroplastic adaptation to pathology framework, emphasizing that to preserve its economy, i.e., function, the brain learns how to cope with the disease by adapting its architecture. Neuroplastic adaptation to pathology is a proposition for a paradigm shift to overcome the shortcomings of traditional psychiatric diagnostic boundaries; this approach can disentangle both the specific pathophysiology of psychiatric symptoms and the adaptation to pathology, thus offering a new framework for both diagnosis and treatment.

Keywords
neuroplasticity, neuroprogression, psychiatric disorders, brain economy, severe mental illness, biomarkers

Introduction
The prevalence, severity, and overall burden of morbidity and mortality represented by psychiatric disorders reflect an urgent global public health priority (Whiteford and others 2013). However, to date, objective measures of psychopathology and biomarkers that reliably delineate normal from disease states, or one disease state from another, are still lacking (Akil and others 2010; Krystal and State 2014). Indeed, for the past 40 years, genomics, neurobiology, cognitive neuroscience, neuroimaging, and pharmacology development have challenged the psychiatric diagnostic nosology boundaries (Krystal and State 2014). Interestingly, the transdiagnostic approach appears as a paradigm shift in the understanding of psychiatric disorders. Indeed, nosological systems, such as the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) and ICD-10 (International Classification of Diseases, 10th Revision), define the different psychiatric disorders as distinct, independent, and categorical constructs (Krueger and Eaton 2015). However, psychiatric diagnosis has always been challenging due to the complexity and heterogeneity of the symptoms that may occur in a particular disorder and the potentially confusing comorbidities with other psychiatric disorders (McHugh 2005).
For several years, the transdiagnostic approach has been developed by focusing on certain clinical dimensions or symptoms such as psychosis (van Os and Reininghaus 2016), anhedonia (Zhang and others 2016), or compulsivity (Gillan and others 2016), with the objective of cutting across existing categorical diagnoses and discerning possible commonalities that may highlight new neurobiological or therapeutic avenues. However, beyond the transdiagnostic approach of symptoms, psychiatric disorders also share the same pattern of longitudinal evolution with courses that tend to be chronic and recurrent (Fusar-Poli and others 2019). This chronic nature is currently studied under the neuroprogression framework, defined as the changes associated with the pathological rewiring of the brain that takes place with the progression of severe mental disorders (Berk 2009). Neuroprogression has been associated with loss of gray matter volume, chronic inflammation, changes in growth factors, oxidative stress, and mitochondrial dysfunction across a range of disorders such as bipolar disorder (BD), major depressive disorder (MDD), or schizophrenia (SCZ) (Berk and others 2011b; Davis and others 2014; Moylan and others 2013).

While considering the plasticity of the brain (i.e., the ability of the brain to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections; Cramer and others 2011), it has recently been suggested that it is necessary to emphasize the bidirectional nature of neuroprogression (Moylan and others 2013). Substantial plasticity and remodeling can then be associated with the evolution of psychiatric disorders, and it becomes necessary to revise the current “deficit-oriented” models (Palaniyappan 2017). Indeed, even if neuroplasticity (NP) was initially thought to be limited to critical periods of brain development, it is now largely accepted that NP occurs throughout the lifespan (Pascual-Leone and others 2005). Several famous neuroimaging investigations demonstrate adaptive neuroplastic modifications in the structure (Draganski and others 2004) and function (Amad and others 2017) of the human brain in response to environmental demands in healthy adults and in patients with psychiatric disorders (e.g., Eack and others 2010; Goldapple and others 2004).

In this article, we review evidence that focuses on alteration of the brain associated with the longitudinal evolution of psychiatric disorders from the perspective of neuroplastic adaptation to pathology. This new concept highlights that substantial plasticity and remodeling may occur beyond the classic neuroprogressive framework.

**Neuroprogression and the Longitudinal Evolution of Psychiatric Disorders**

The concept of “neuroprogression” has been proposed to account for changes observed through the natural course of psychiatric disorders (Kapczinski and others 2014). This concept finds its origins in Europe during the mid-19th century, when Jean-Pierre Falret, Karl-Ludwig Kahlbaum, and Joseph Guislain developed the idea of a longitudinal evolution of psychiatric disorders, even until recovery, and emphasized the importance of including longitudinal factors in psychiatric diagnosis. In 1867, Wilhelm Griesinger described these emerging conceptions of neuroprogression as “a constant progressive course, which may proceed even to complete destruction of the mental life” (Griesinger 1867, p. 207). These historical observations of patients presenting with early stages of discrete symptoms that move toward progressive alterations are still relevant with staging models going from very early stages defined by at-risk or latency stages to late or end-stages (Scott and others 2013) (Fig. 1). Neuroprogression has been associated with not only chronic but also recurrent courses. Indeed, psychiatric disorders (e.g., MDD, BD, SCZ, panic disorder [PD], obsessive-compulsive disorder [OCD], anorexia nervosa) show very high relapse rates, and each episode of illness increases the likelihood of future episodes, a phenomenon also known as kindling (Post 2007) (Table 1). Similar mechanisms seem to be involved in addictive disorders with significant changes in neural circuitry mediating the motivational system as the disorder progresses, which could drive compulsive drug taking and narrowing the behavioral repertoire to drug seeking (Koob and Moal 2005). BD is probably the disorder that has been the most studied from the perspective of neuroprogression. BD is a recurrent chronic disorder characterized by fluctuations in mood state and energy affecting more than 1% of the world’s population (Grande and others 2016). In BD, increased recurrences are associated with a risk of rapid cycling between the depressive and manic states (Berk and others 2011a). This stepwise progression exists not only in clinical symptoms but also in treatment response, neurobiology, and functional impairment (McGorry and others 2010). Berk developed the concept of “pathological rewiring of the brain” to explain the links between clinical evolution of BD and the underlying neuroprogression (Berk 2009). This approach finds its roots in the neurosensitization model proposed by Post and the allostatic load hypothesis by Kapczinski and others (Kapczinski and others 2008; Post 1992). The neurosensitization model postulates that sensitization to both stressors and episodes leads to alterations of neuronal activities that may be transduced at the gene expression level (e.g., the protooncogene c-fos and related transcription factors) (Post 1992). These biochemical and anatomical parameters evolve over time as a function of recurrences and lead to poorer pharmacological responses in affective disorders (Post 1992). The allostatic load hypothesis suggests a direct modulation of brain circuits by stress and episodes leading the patients to become...
Figure 1. The clinical staging model proposed that major psychiatric disorders develop from an “at-risk” asymptomatic state, through an initial stage of undifferentiated general symptoms (e.g., mild anxiety, sleep disturbance, depressive symptoms) (stage 1), followed by a worsening of these existing symptoms and the acquisition of new symptoms, associated with greater syndromal specificity and with behavioral and functional decline. Further progression of illness may then take place, resulting in the occurrence of a first episode of a full-threshold syndrome(s) (stage 2), which may be followed by the development of recurrent or persistent symptoms (dotted lines) (stage 3) or even severe, treatment-resistant illness (stage 4). Interactions, between endogenous (e.g., genes) and exogenous (e.g., drug, urbanicity, social relationships, rhythms) factors, influence the risk of developing a psychiatric disorder as well as the recurrence and persistence of symptomatic episodes.

Table 1. Clinical Characteristics of Psychiatric Disorders or Symptoms from the Perspective of the Repetitiveness and Rates of Recurrence or Relapse.

| Disorder                | Rate of Relapse and Clinical Aspect of Repetitiveness                                                                                                                                 |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Depressive disorder     | • Highly recurrent disorder (Moylan and others 2013)  
                          • The risk of recurrence after a first major depressive episode is 50% and increases with subsequent episodes (Kendler and others 2000; Post 1992)  
                          • Individuals with a history of depression will have five to nine separate episodes in their lifetime (Burcusa and Iacono 2007) |
| Schizophrenia           | • Long-term course of illness is typically characterized by multiple relapses, persistence of symptoms, and enduring cognitive and functional deficits (Andreasen and others 2005)  
                          • 60% to 90% of relapses occur within 2 years of a first psychosis episode after treatment reduction/discontinuation (Emsley and others 2013)  
                          • 30% have auditory hallucinations that are resistant to treatment (Shergill and others 1998) |
| Bipolar disorder        | • Highly recurrent disorder: 60% relapse 2 years after a major episode (Gitlin and others 1995)  
                          • In patients receiving treatment according to contemporary practice guidelines, 58% achieve recovery and 49% develop recurrences over a 2-year period (Perlis and others 2006)  
                          • Patients change symptom status (asymptomatic, subthreshold levels, full-blown major depression, and mania) an average of six times per year and polarity (full-blown major depression or mania) more than three times per year (Judd and others 2002) |
| Panic disorder          | • Recurrent panic attacks (Roy-Byrne and others 2006)  
                          • Recurrence rate of 25% 2 years after remission (Scholten and others 2013) |
| Obsessive-compulsive disorder | • Recurrent and persistent thoughts and repetitive behaviors (Abramowitz and others 2009)  
                               • 60% relapse 5 years after remission (Eisen and others 2013) |
more vulnerable to subsequent environmental stressors, drug abuses, and symptomatic episodes (Kapczinski and others 2008). Numerous biochemical mediators underlying this neuroprogression and stress sensitization have been found to be involved, such as inflammatory processes (including the CRP [C-reactive protein], interleukin [IL]-6, IL-10, and TNF-α [tumor necrosis factor-α]), neurotrophins (including the peripheral blood BDNF), and oxidative stress processes (including the glutathione system; Berk 2009; Munkholm and others 2016).

Neuroprogressive features have also been observed in other psychiatric disorders. MDD is associated with poorer symptomatic, treatment, and functional outcomes in patients with earlier disease onset and an increased number and length of depressive episodes (Table 1) (Moylan and others 2013). Stage-related structural brain changes such as a reduced hippocampal volume are influenced by illness duration, age of onset, and episode frequency in patients with MDD (Eker and Gonul 2010). Moreover, it has been shown that multiple biochemical pathways (inflammation, stress axis, oxidative stress, disturbance to mitochondrial energy production and cell survival mechanisms, and gene transcription alterations) interact simultaneously to cause cellular damage that underwrites the neuroprogression in MDD (Moylan and others 2013).

Schizophrenia is also characterized by neuroprogressive features at clinical and neurobiological levels (Davis and others 2014). Indeed, SCZ has been associated with progressive enlargement of brain ventricles (Van Haren and others 2012) mediated by abnormalities in the cortical gray matter and reductions in white matter surface area (Colibazzi and others 2013; Vita and others 2012). These changes may correlate with symptoms and disorder progression (Vita and others 2012). Like BD and MDD, SCZ has been associated with chronic inflammation, oxidative stress, and mitochondrial dysfunction (Davis and others 2014).

In summary, there is a growing scientific literature observing that multi-scale changes (from behavior to molecular levels) appear during the evolution of psychiatric disorders, from very early “at-risk” phases to different major clinical stages (McGorry and others 2014; Scott and others 2013). These changes may be the consequence of neuroprogression processes that lead to more permanent alterations in late stages. However, it is necessary to consider and emphasize the bidirectional nature of this neuroprogression: substantial plasticity and remodeling can occur (Moylan and others 2013), especially in light of the concept of the economy of the brain.

The Economy of the Brain

The brain is more than an intricate network of neurons connected in an immutable fashion; it is capable of adaptation to its internal and external environment, which endows it with great resilience as a system. Its structure and function continuously change throughout the lifespan of an individual, sometimes drastically due to injury or illness (Bullmore and Sporns 2012). From this perspective, several coherent brain models have been proposed (see, e.g., Friston 2009; Turner 2019). Here we focus on neuroplasticity, which is, as described earlier, arguably one of the key mechanisms that has enabled humans to survive and adapt as a species. In this section, we argue that it is this same capacity for learning and adaptation that may be responsible for the brain’s demise in chronic psychiatric disorders.

In this article, we contrast brain evolution and brain adaptation. Brain evolution is the process that has led to general structural and functional organization of the normal brain via genetic mutations and natural selection (Somel and others 2013). Brain adaptation, on the other hand, refers to the changes the brain undergoes post fertilization, either via normal aging or in response to changes in its environment and integrity such as learning, trauma, or, as we argue here, psychiatric disorders (Amad and others 2017; de Kloet and others 2005).

With the principle of least action guiding the evolutionary process, we can safely assume that the healthy brain is currently the most energy-economic version of the system that yields healthy brain function (Hutto 1999) within an approximately constant energetic budget (Raichle and Gusnard 2002). In the awake state, the available evidence suggests that the adult brain’s overall energy consumption is remarkably stable over time. The adult brain continuously consumes large amounts of energy (~20% of the resting total body O2 consumption) regardless of whether one is engaging in a cognitively or emotionally demanding task or simply resting with their eyes open (Messier 2004; Raichle and Gusnard 2002; Siegel 1999; Sokoloff and others 1955). Most of this baseline energy expenditure is thought to be required for maintaining ion flux related to excitation and conduction (Siegel 1999). Although the neurons activated during a specific cognitive task do require extra blood, oxygen, and glucose, local increases in energy consumption are very small compared with the brain’s large baseline intake, and are typically accompanied by activity decreases in neighboring areas (Leech and others 2014; Raichle and Gusnard 2002). As a result, it is argued that in the awake state global brain metabolic expenditures are approximately constant and brain dynamics are close to an optimal state, that is, a “sweet spot” (Expert and others 2011), allowing the maximal response range (Kinouchi and Copelli 2006) while reducing energy expenditures incurred by the structural and functional architecture of the brain (Bullmore and Sporns 2012; Chialvo 2010).
The preservation of homeostasis within the brain’s energetic budget is paramount to keeping brain dynamics in this operating “sweet spot” and occurs at the global level, with evidence showing that the brain is operating close to an attractive critical point (Expert and others 2011) that allows for a trade-off between segregation and integration. This phenomenon has been proposed as a basis for a model that reconciles multi-level brain function findings in health and in psychiatric disorders such as SCZ (Turkheimer and others 2015). The neurobiological underpinnings of critical brain dynamics are not fully understood, but the available evidence suggests that a complex synergy between the organization of the brain’s structural connectome and the excitation-to-inhibition balance in local neuronal populations is likely at play (Froemke 2015; Lord and others 2017; Shew and others 2011). One of the consequences of a system being close to criticality is the similarity of processes at different levels of description. In the case of homeostasis, this similarity is reflected by the synaptic adaptation hypothesis (Tononi and Cirelli 2014), which states that sleep is paramount to regulating synaptic adaption to learning. Synaptic plasticity forms the basis for brain adaptability and our capacity to learn, and these structural changes are also reflected by functional brain changes, which provides a self-similar causality chain from micro- to macroscopic scales (Amad and others 2017; Turkheimer and others 2015).

We propose that certain psychiatric disorders are effectively the result of a brain adaptation mechanism akin to learning. The basis of our argument lies in the brain economy framework, which implies that the brain tries to remain as close as possible to its optimal state (Bullmore and Sporns 2012; Expert and others 2011). We regard the endogenous and/or environmental perturbations linked to the onset of chronic psychiatric disorders as long-term disturbances to normal brain function that are constantly pushing the brain economy away from its optimal healthy state (Roth and others 2009; Rutten and Mill 2009). This phenomenon leads the brain to develop compensatory mechanisms to adapt and preserve the performance of cognitive and behavioral outputs as much as possible and has been associated with the prodromal state of a psychiatric disorder (Lord and others 2011; Lord and others 2012) where, notably, functional connectivity (FC) networks may alter their topology in response to illness to preserve cognitive and behavioral output. However, these resulting new functional pathways may not be optimally supported by the structural connectome and be energetically costly to maintain over time. We therefore hypothesize that these compensatory mechanisms are not sustainable in the long term and that the brain economy becomes overstretched as more energy has to be spent to maintain the most essential regulatory, cognitive, and motor outputs needed for survival (i.e., “baseline” energy expenditure). This compensation therefore increases the baseline energy expenditure and leaves less energy available to carry out more complex cognitive operations that are useful, but not essential for survival (i.e., studying for an exam, planning a trip). This last point is a direct consequence of the maximum energy expenditure of the brain being relatively constant, as outlined above. It is indeed well documented that an increase activity in a brain region has to be matched with either a global or local decrease in energy expenditure (Allison and others 2000; Huang and others 1996; Leech and others 2014; Shmuel and others 2002; Shmuel and others 2006; Tootell and others 1998). In the neuroprogression framework, maintaining homeostasis implies that the brain then has to adapt to the disease and restore brain economy to a less expensive state, given the constraints of the disease and its progression via synaptic plasticity mechanisms akin to learning. This full adaptation means that new structural pathways are created to learn to “cope” with the illness while preserving as much as possible of the brain function and associated cognitive and behavioral outputs. At the same time, it also means that normally used pathways are abandoned over time, which is consistent with numerous imaging studies that find overactivation and underactivation patterns in the brain networks or “connectome” (Crossley and others 2014; Crossley and others 2016), as well as concurrent increases and decreases in FC with conservation of cognitive outputs (Crossley and others 2014; Crossley and others 2016; Lord and others 2011; Lord and others 2012). Once the brain economy is restored with respect to the new functional and structural organization, the brain finds itself in a new “optimal” yet diseased state, and the process is complete. In other words, to preserve its economy, that is, functional dynamics and behavior, the brain learns how to cope with the disease by adapting its structure. The new optimal state requires a higher baseline energy expenditure and therefore has less energy to spend to perform more complex tasks, making it more difficult to maintain cognitive outputs; a recent study shows that the exploration of brain states related to cognitive control of remitted MDD patients is significantly reduced compared with controls (Figueroa and others 2019).

Let us now formalize our proposal illustrated in Figure 2. The simplest model of the brain interacting with its environment consists of a semi-black box that takes inputs and produces outputs. Let us now restrict ourselves to a given set of inputs $I$, the brain then produces a set of corresponding outputs $O$, using its anatomical wiring and the function it supports, for a given energetic price $E$. We denote the set of output expected from a healthy individual and the associated energy as $O^h$ and $E^h$, respectively. One way to assess the mental state of a
subject is to test his/her answers and/or behavioral responses to a pre-established set of items on the basis of which he/she will be deemed ill, at-risk, or in the healthy range. In our language, this means that if the outputs from a subject deviate more than a given quantity, that individual will be classified as prodromal, diseased, and so on, and we denote such outputs as $O_d$ and an associated energy expenditure $E_d$. As reviewed in the next section, functional and structural dysconnectivity have been shown to be present in many psychiatric diseases, and we hypothesize that structural connectivity (SC) and FC indeed deviate from the healthy control baseline in patients (see Fig. 3).

The total energy at the brain disposal is approximately constant and regulated by homeostasis, and our argument posits that, within this energetic budget, compensatory mechanisms will try to preserve the outputs as close as possible to the healthy range in response to exogenous and/or endogenous constraints, doing so by adapting first brain function (FC) and then its structure (SC), at the cost of an increased energy expenditure.

We thus have two quantities that depend on SC and FC, the outputs $\{O\}_{i} (SC_i, FC_i)$ and the energy expenditure $E(SC_i, FC_i)$. These values define the brain economy index (BEI), which measures the deviation of the brain economy of a state $i$ from a healthy state by combining the quality of the brain outputs and its energy expenditure as follows:

$$BEI (\{O\}_{i}, E) = \alpha \|O\|_h - \{O\}_{i} \| + \beta E_h - E_i$$

The constants $\alpha$ and $\beta$ weight the two contributions and ensure that the BEI is dimensionless. We want to highlight at this point that the present model derived from

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**Figure 2.** The brain economy paradigm posits that the brain minimizes energy expenditure for a specific functional and structural configuration (FSC). The brain economy index (BEI) then represents a measure of optimality of brain function with respect to energy expenditure and cognitive outputs that is minimized for a healthy FSC. Blue circles: current FSC; Empty circles: locally optimal FSC; Red arrows and links: endogenous and exogenous factors affecting the FSC; Green arrows and links: compensatory mechanisms that try to maintain the FSC into its local optimal. The $x$-axis corresponds to possible FSC, and the $y$-axis corresponds to the associated BEI that takes into account energy expenditure and cognitive outputs of the corresponding FSC. (A) The brain is currently in its optimal healthy FSC condition, and any perturbation would put strain on it. (B) Endogenous and exogenous factors put stress on the FSC and push it away from its optimal point, while compensatory mechanisms try to counter these effects. The compensatory mechanisms cause increased energy expenditure, while perturbating factors cause decreases in cognitive outputs. (C) When the perturbative factors are stronger than the compensatory mechanisms, as in (B), the compensatory mechanisms overstrain the brain FSC and eventually lead to a breakdown (e.g., first psychotic episode) and a reconfiguration and relaxation of the system, dominated by the compensatory mechanisms, into a new FSC that will be locally optimal, that is, lower energy expenditure than during intense straining and suboptimal, but comparatively improved, cognitive outputs. (D) The FSC has settled and adapted to its new local optimum. Being less optimal than the healthy FSC, the new FSC is less stable. (E) Lower barriers, particularly in the direction of worsened symptoms/state, make it more difficult for compensatory mechanisms to contain further endogenous and exogenous perturbations. This phenomenon leads to faster recurrence associated with increasingly worse subject cognitive outputs.
The framework introduced here is the simplest formulation that we can justify with the existing literature and aims at being a basis to be enriched as new experimental facts come to light.

We now present Figure 2 to show how the BEI can be used to characterize the evolution and chronicity of psychiatric diseases. In this figure, each minimum corresponds to a combination of FC, SC, and $O_i$, with the deeper one corresponding to the healthy baseline. Disease-associated exogenous and/or endogenous perturbations will first lead to a modification of FC patterns to maintain $O_h$, at the cost of an increased energy expenditure, raising the BEI (panel B). When the brain metabolism becomes overstretched, a symptomatic episode occurs, and the system moves into a new basin of $O_d$. The corresponding outputs are no longer on par with the healthy baseline but allow the energy expenditure to decrease, while reinforcing the changes in FC (panel C) and eventually leading to change in the SC via synaptic plasticity mechanisms, when the system reaches a new minimum of the BEI, as expected from the economy of the brain theory. This new minimum is higher than the healthy baseline because of SC and FC changes and the associated pathological outputs $O_d$ (panel D). This new minimum is more unstable than the original healthy minimum because its BEI is closer to the level at which disease-related episodes occur. Therefore, the process is more prone to repeating itself, leading to more frequent episodes and disease progression over time (panel E).

**Highlighting the Plastic Adaptation to Pathology with Neuroimaging**

In this section, we aimed to view brain MRI (magnetic resonance imaging) evidence that can be interpreted from the perspective of the neuroplastic adaptation to pathology.

**Structural MRI**

Neuroimaging evidence shows both differences in structural features associated with their relevant functions and changes in structural features (gray matter volume and cortical thickness) when long-term neural activity patterns are changed by experience. These changes probably involve many coordinated brain regions that can be explored with the study of changes in the white matter pathway microstructure and the study of white matter connectivity with diffusion tensor imaging (DTI) (Fig. 3). Common measures of DTI include fractional anisotropy (FA), reflecting anatomical white matter features such as axon caliber and myelination. The interpretation of variations in FA is not straightforward; however, a reduced FA is commonly interpreted as a loss in white matter integrity, whereas an increased FA is thought to reflect an increase in white matter connectivity (Dong and others 2004). Many structural neuroimaging studies have thus shown not only a loss of matter in brain volumes among patients suffering from neuropsychiatric disorders; brain volume increases have also been demonstrated in psychiatric disorders such as SCZ, BD, autism, or OCD.
In SCZ, gray and white matter reductions are well documented (Hajjma and others 2013). However, the recent study of van Erp and others (van Erp and others 2016) involving more than 2000 patients with SCZ showed that compared with controls, individuals with SCZ exhibited significantly larger pallidum volumes. Interestingly, duration of illness and age were positively associated with pallidum and putamen group contrast effect size. Nonetheless, as highlighted by the authors, these changes may reflect the cumulative effects of antipsychotic medication treatment on basal ganglia volumes reported especially for the putamen (Gur and others 1998; Li and others 2012), even if a disease-related age effect cannot be excluded because larger pallidum volumes in unmedicated, non-ill relatives of individual with SCZ have also been reported (Oertel-Knöchel and others 2012; Yang and others 2012).

In BD, a meta-analysis of gray matter abnormalities using voxel-based morphometry studies revealed that in chronic patients, longer duration of illness was associated with increased gray matter in a cluster that included the basal ganglia, subgenual anterior cingulate cortex, and amygdala (Bora and others 2010).

In OCD, increased gray matter volume has been demonstrated in the basal ganglia (putamen and caudate) (Radua and Mataix-Cols 2009; Radua and others 2010; Rotge and others 2010; Zarei and others 2011), the thalamus (Kim and others 2001), and cortical regions such as left orbital frontal gyrus, right middle frontal gyrus, left middle temporal gyrus, precentral gyrus, and postcentral gyrus (Tang and others 2016). Bilateral cerebellar volume increases and age-related increases in putamen, insula and orbito-frontal cortex volumes have also been reported in a recent mega-analysis (de Wit and others 2014).

In autism, increased gray matter volumes are well known and replicated findings in regions including areas of the temporal and parietal lobes (Yang and others 2016).

Finally, in social anxiety disorder, Talati and others demonstrated that compared with healthy controls, patients exhibited greater gray matter in the left parahippocampal and middle occipital, bilateral supramarginal and angular cortices, and left cerebellum (Talati and others 2013). For other anxiety disorders, Shang and others showed increased gray matter volumes in the right dorsolateral prefrontal cortex in drug-naive patients with comorbid depression-anxiety (Shang and others 2014).

Functional MRI and Functional Connectivity

Neuropsychiatric disorders are often coined as dysconnectivity syndromes (Buckholtz and Meyer-Lindenberg 2012). The dysconnectivity hypothesis suggests that the existence of impaired connectivity between different brain regions is responsible for abnormal functional integration within neural networks. This impaired connectivity might be associated with an impaired control of synaptic plasticity (Stephan and others 2009). The underlying mechanisms for dysconnectivity remain unknown but likely involve both genetic (Brennand and others 2011) and environmental factors (Sullivan and others 2003), leading to early alterations in the development of brain wiring and impaired experience-dependent synaptic plasticity (Stephan and others 2006). Recently, resting-state FC analyses have been widely used to investigate neuroplastic modifications (Fig. 3). FC corresponds to the temporally correlated, low-frequency spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals across brain regions that occur when a participant is not performing an explicit task (Fox and Raichle 2007). These temporal correlation patterns are not random, and specific networks, such as the default mode network (Greicius and others 2003), have been reliably identified across studies and participants. Moreover, it is now widely accepted that the strength of correlations within and between networks has behavioral relevance (Guerra-Carrillo and others 2014). Interestingly, it has been proposed that FC is an effective measure of plasticity and that activity patterns reflect the history of repeated synchronized activation between brain regions (Guerra-Carrillo and others 2014).

Consistent with the bidirectional nature of the plastic adaptation to pathology outlined above, neuroimaging investigations of FC in psychiatric disorders often reveal not only a loss of FC but also concurrent FC increases in specific neural circuits (Crossley and others 2014; Crossley and others 2016; Lord and others 2011; Lord and others 2012). Importantly, the reported FC increases have been shown in many studies to correlate with the clinical expression of the disease, which suggests that increased FC, as decreased FC, is a pathologically informative feature of brain networks in neuropsychiatric disorders.

In SCZ, a number of studies have found connectivity increases across several brain systems, including the default mode network, cortico-striatal, and thalamocortical pathways (Fornito and Bullmore 2015; Whitfield-Gabrieli and others 2009). Furthermore, in many cases, these FC increases have been positively correlated with symptom severity (Anticevic and others 2014; Fornito and others 2013; Hoffman and others 2011; Whitfield-Gabrieli and others 2009). A recent meta-analysis of 52 seed-based voxel-wise resting-state FC studies showed that SCZ was characterized not only by hypo-connectivity within multiple networks but also by hyper-connectivity between the affective network and the ventral attention network (Dong and others 2018). Interestingly, a brain-wide FC study in 789 participants (343 patients) recently
showed stage-specific functional dysconnectivity across first-episode and chronic stages of SCZ. In first-episode patients, 90% of the functional connectivity changes (from healthy controls) involved the frontal lobes (including Broca’s area), whereas for chronic patients, functional connectivity differences extended to wider areas of the brain, including not only reduced thalamo-frontal connectivity but also increased thalamo-temporal and thalamo-sensorimotor connectivity (Li and others 2017).

FC increases have also been reported in mood disorders including BD and MDD. Patients with BD notably show greater connectivity between the amygdala and frontal cortical structures including the anterior cingulate cortex and medial prefrontal cortex compared with healthy subjects (Brady and others 2016; Cerullo and others 2012; Favre and others 2014), which, in turn, has been correlated with the duration of the disease. In MDD, patients show increased FC in the default mode network (Goya-Maldonado and others 2016; Greicius and others 2007), which notably correlates with the number of depressive episodes. Increased fronto-striatal connectivity between the caudate and dorsal prefrontal cortex has also been found in MDD and is positively correlated with the severity of the disorder (Furman and others 2011). Hyper-connectivity between the anterior temporal and subgenual cortices is also a risk marker of subsequent recurring depressive episodes in MDD patients (Lythe and others 2015).

Finally, increased FC has also been found in other disorders such as autism spectrum disorder (ASD) or anorexia nervosa (AN). Individuals with ASD showed increased FC between primary sensory networks and subcortical networks (thalamus and basal ganglia), and the strength of such connections was associated with the severity of autistic traits in the ASD group (Cerliani and others 2015). Additionally, in AN, increased FC has been observed at rest in the fronto-parietal network, supporting the hypothesis of excessive cognitive control in AN, and of the anterior insula with the default mode network, which may reflect the high levels of self- and body-focused ruminations (Boehm and others 2014).

Neuroimaging evidence in psychiatric disorders such as SCZ, BD, autism, or OCD highlights the plastic adaptation to pathology, with many structural and functional neuroimaging studies observing that there is not only a loss of matter in different brain region volumes or decreased FC but also brain volume increases, along with structural and FC increases or decreases across brain regions. Interestingly, these changes of volume and connectivity are associated with anatomo-clinical correlates, including the disorder progression, the number of episodes of illness, and the duration of disease, highlighting the role of dysconnectivity processes in the adaptation to pathology.

The Neuroplastic Adaptation to Pathology Framework

After having highlighted the high rates of recurrence or relapse in psychiatric disorders from the neuroprogressive perspective, the constraints on the brain economy function, and the increases in brain volume and structural and/or FC that may be associated with the clinical features and duration of most major psychiatric disorders, we thus propose to integrate this evidence in the framework of neuroplastic adaptation to pathology. Adaptation to pathology can be defined as “the plastic modification of the brain associated with the longitudinal evolution of psychiatric disorders whose courses tend to be recurrent and progressive; with a very high rate of relapse, each episode of illness increases the likelihood of future episodes” (Table 1). Indeed, the brain is essentially a plastic organ, and it is now well known that the repetition of nearly all motor and cognitive skills and processes leads to structural and functional neuroplastic modifications, strengthening those pathways (Amad and others 2017; Draganski and others 2004; Linden 2006). Considering the intensity, duration, and repetition of psychiatric episodes (Bremner 2006; Pol and Kahn 2008), we believe that the brain will also adapt to these episodes. Moreover, the repetition of cognitive or motor skills is known to be executed faster the more they are practiced as a result of neuroplastic changes, until behaviors are executed habitually or automatically in a manner that consumes fewer neural resources, a natural consequence of the brain economy framework (Ashby and others 2010). Based on these observations, we propose a neuroplastic theoretical framework that posits that patients with psychiatric disorders are unfortunate “pathological experts.” The repetition of psychiatric episodes and/or symptoms then leads to experience-dependent neuroplastic modifications that increase the likelihood of future episodes and/or symptoms, which ultimately leads to a neuroplastic vicious circle associated with increases in repetitiveness and decreases in behavioral flexibility (Graybiel 2008), regardless of extrinsic environmental triggers.

From the perspective of the plastic adaptation to pathology, the review of neuroimaging studies presented in this article highlights the importance of the basal ganglia and cortical-subcortical connectivity, which appear to be associated with the longitudinal course of psychiatric disorders. The basal ganglia are a set of deep forebrain nuclei consisting of the striatum (caudate and putamen), globus pallidus (internal and external segments), subthalamic nucleus, and substantia nigra (pars reticulata and pars compacta). Interestingly, repetitive behaviors or repetitive cognitive activities are supposed to emerge as a result of experience-dependent plasticity in different basal ganglia-based circuits (Ashby and
others 2010) connected to other brain regions, including the cerebral cortex, thalamus, several brainstem nuclei, and the cerebellum, to form a network with both open- and closed-loop circuitry (Caligiore and others 2017). Thus, although further investigation is required, we believe cortical-subcortical and cerebellum networks related to learning and habits could play a major role in the repetition of episodes of illness involved in psychiatric disorders (Graybiel 2008).

The neuroplastic framework presented here fits well with the dysconnectivity model of psychiatric disorders, which postulates that psychiatric symptoms are associated with impairments in structural and functional brain connectivity in the networks that underpin the functions of everyday human experience (i.e., the cognitive, affective, motor, motivational, and social networks) (Buckholtz and Meyer-Lindenberg 2012). Abnormal connectivity (decreased or increased) between brain areas is associated with impaired control of synaptic plasticity and its underlying mechanisms, which involves both genetic and environmental factors and leads to alterations in brain wiring and impaired experience-dependent synaptic plasticity (Amad et al. 2014a; Stephan and others 2006). Thus, rather than the flexible networks with interactions within and between populations of neurons that allow for efficient communication in healthy subjects, patients with psychiatric disorders are characterized by rigid dysconnectivity of the neural networks (Buckholtz and Meyer-Lindenberg 2012). In our framework, the strength of this dysconnectivity is reinforced by the repetition and duration of psychiatric symptoms or episodes (Fig. 2).

Discussion

The framework of adaptation to pathology is a paradigm shift that leads to a novel conceptualization of the pathophysiology of psychiatric disorders and emphasizes the influence of neuroplastic adaptations to symptom repetition that are inherent to the brain’s ability to adapt (Pascual-Leone and others 2005). We believe that this framework could make it possible to disentangle the specific pathophysiology of psychiatric symptoms, on the one hand (Buckholtz and Meyer-Lindenberg 2012), and the pathophysiology of the adaptation to pathology, on the other hand (Fig. 2). Fascinatingly, two large-scale systematic meta-analyses of structural MRI and task-fMRI studies across multiple psychiatric diagnoses failed to identify diagnosis-specific effects (Goodkind and others 2015; Sprooten and others 2016). It was then suggested that the abnormalities in brain regions and networks observed in individual MRI studies may reflect brain disorder-general conditions that facilitate the emergence and persistence of symptoms but are insufficient to explain symptomatic variability across disorders (Sprooten and others 2016).

The plastic adaptation to pathology also provides a natural framework encompassing the neuroprogression hypothesis. As it has been specifically suggested for schizophrenia, we support the view that progressive changes in psychiatric disorders may not represent a deficit or decompensation process per se but that they could be the result of a distributed, nevertheless inefficient, multi-scale reorganization response (Palaniyappan 2017). Moreover, the concept developed here is a natural consequence of the economy of the brain and fits with the dysconnectivity model of psychiatric disorders. Consideration of the adaptation to pathology framework should aid the integration of the vast and complex translational data across the genomic, neuronal, and behavioral levels. Indeed, it is essential to leverage novel methods for finding patterns and structure in complex, multi-scale datasets from big data and complexity science to develop methodological frameworks to test clinically relevant hypotheses.

The same idea, developed here from a neuroimaging perspective, can then be developed with the genetic approach of psychiatric disorders. Indeed, even if the heritability of psychiatric disorders is important, most genes are shared between disorders, and few genes have been strongly associated with these disorders (Brainstorm Consortium and others 2018). We believe that in one disorder, several genetic pathways interact, involving pathways associated with the development of symptoms and pathways associated with the plastic adaptation to pathology. Thus, vulnerability in the genetic pathway involved in plastic adaptation to pathology may represent risk factors for the repetition of episodes more than the risk for the development of symptoms. Those genes could correspond to plasticity genes modulating the susceptibility to external and internal environment instead of vulnerability genes that would increase the risk of developing symptoms (Amad and others 2014b). The integration of genetic pathways to the framework of the brain adaptation to pathology could help explain the individual variability of vulnerability regarding relapses and chronicity.

Finally, the plastic adaptation to pathology framework should be considered in future fundamental and clinical studies to overcome the scientific and public health challenges posed by psychiatric disorders. To test this framework, scientific methods should not only focus on the differences between patients and disorders but also develop approaches to highlight the factors that are shared within and/or between psychiatric disorders (i.e., a transdiagnostic approach) (Table 2). For example, large brain imaging data sets from patients with different disorders (e.g., schizophrenia, MDD, BD) could be analyzed using methods such as machine learning or pattern recognition to look for connectivity patterns shared by different disorders and associated with the number of episodes or duration of disease. In these studies, multimodal
Neuroimaging should be used to quantify the degree of reorganization to grade the severity of the underlying pathophysiological process (Palaniyappan 2017). Additionally, as clinical and functional outcomes are not always stable at an individual level, patients should be assessed at the symptom level across time to provide appropriate variables to study in the plastic adaptation to pathology framework (Palaniyappan 2017). Interestingly, the bidirectional nature of neuroprogression of psychiatric disorders should be tested specifically. Indeed, one of the main alternatives to the framework exposed here could correspond to an absence of homeostasis and to a violation of brain economy principles in patients with psychiatric disorders. In this case, neuroprogression could then be associated with an inexorable energy loss characterized by a lack of neuroplasticity and remodeling in this vulnerable group (See Summary Table 3).

The identification of adaptation to pathology processes in psychiatric patients will be clinically useful, particularly for understanding the high frequency of treatment-resistant psychiatric disorders and explaining why these disorders should be treated as rapidly as possible to prevent self-reinforcement of the pathological network (Sarpal and others 2017; Scott and others 2013). Indeed, this framework suggests that therapeutic interventions should occur as early as possible. At all stages, interventions should aim to prevent relapse and episodes by using course alteration interventions to target the neuroprogression causing a disorder to stop and, ideally, reverse its progression (Millan and others 2016). For each stage, specific interventions should be developed to treat both processes underpinning current symptoms (symptomatic treatment) and the plastic adaptation to pathology (treatment targeting pathological networks). Whereas many symptomatic pharmacological and nonpharmacological treatments are effective in psychiatric disorders, these interventions should be guided by diagnosis for each stage with previously highlighted limits of the traditional psychiatric diagnostic system (McGorry and others 2014). Thus, biomarkers research is expected to be able to disentangle the stages of this common progression of adaptation to pathology in psychiatric disorders. Highlighting the common patterns of psychiatric disorders that are associated with adaptation to pathology would allow us to better target and design treatments by considering them as etiological or symptomatic. Indeed, psychotropic treatments are effective for numerous conditions, for example, the antidepressants used to treat depressive disorder are also efficacious for PD, OCD, and posttraumatic stress disorder, likely because they stop a vicious circle of dysconnectivity reinforcement (i.e., symptomatic treatment) rather than targeting the initial pathophysiology of the disorder (i.e., etiologic treatment). Nonpharmacologic treatments such as cognitive behavioral therapy or physical exercise are also known to enhance brain plasticity and should be considered as add-ons to counteract the plastic adaptation to pathology (Rief and others 2016). Interestingly, the neuroscience of brain...
plasticity provides new insights into how to drive “corrective” changes in impaired brains via intensive training that could help hinder and even reverse the adaptation to pathology (Merzenich and others 2014). Finally, circuit-specific interventions targeting pathological networks could be promising strategies (Downar and others 2016), especially when taking the degree of brain reorganization following adaptation to pathology into account.

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