

## REVIEW

# Molecular and Epigenetic Mechanisms for the Complex Effects of Stress on Synaptic Physiology and Cognitive Functions

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## Abstract

Evidence over the past decades has found that stress, particularly through the corticosterone stress hormones, produces complex changes in glutamatergic signaling in prefrontal cortex, which leads to the alteration of cognitive processes mediated by this brain region. Interestingly, the effects of stress on glutamatergic transmission appear to be “U-shaped,” depending upon the duration and severity of the stressor. These biphasic effects of acute vs chronic stress represent the adaptive vs maladaptive responses to stressful stimuli. Animal studies suggest that the stress-induced modulation of excitatory synaptic transmission involves changes in presynaptic glutamate release, postsynaptic glutamate receptor membrane trafficking and degradation, spine structure and cytoskeleton network, and epigenetic control of gene expression. This review will discuss current findings on the key molecules involved in the stress-induced regulation of prefrontal cortex synaptic physiology and prefrontal cortex-mediated functions. Understanding the molecular and epigenetic mechanisms that underlie the complex effects of stress will help to develop novel strategies to cope with stress-related mental disorders.

**Keywords:** stress, corticosterone stress hormones, glucocorticoid receptor, prefrontal cortex, glutamatergic transmission, AMPA receptor, NMDA receptor, trafficking, protein ubiquitination, stress-related mental disorders, cognition, emotion, histone deacetylase, E3 ligase

## Introduction

Trauma or stressful events across the lifespan are associated with many medical comorbidities, such as cardiovascular and immunological illnesses (de Kloet et al., 2005; McEwen, 2008; Iwata et al., 2013). Stress is also a critical predisposing factor for psychiatric disorders, including depression, anxiety, post-traumatic stress disorder, and schizophrenia (Agid et al., 1999; Pittenger and Duman, 2008; McEwen and Morrison, 2013). Corticosteroid, the major stress hormone, plays a key role in emotional and cognitive regulation in the CNS. Interestingly, it induces a “U-shaped” effect to maintain brain homeostasis

(Diamond et al., 1992; Joels, 2006). Acutely released or moderate levels of corticosteroid mediate a “flight-or-fight” adaptive response in threatening situations. On the other hand, chronically present or high levels of corticosteroid are considerably harmful to brain functioning and are associated with the maladaptive changes in disease processes (Joels, 2006).

It has been believed that genomic mechanism of corticosteroid is responsible for the delayed and long-lasting effect of stress (de Kloet et al., 2005). Mineralocorticoid and glucocorticoid receptors, the major subtypes of corticosteroid receptor,

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## Significance Statement

Stress, by activating corticosterone stress hormones, produces profound and diverse effects on cognition and emotion. This review summarizes the key molecules involved in the stress-induced regulation of prefrontal cortex (PFC) synaptic physiology and PFC-mediated functions. Revealing the molecular and epigenetic mechanisms that underlie the complex effects of stress will help to understand the multifaceted role of stress in mental health and disorders.

are also ligand-driven transcription factors. Binding of corticosteroid triggers nuclear translocation of the receptor and subsequently influences the expression of genes involved in stress-mediated pathway (Beato and Sanchez-Pacheco, 1996; Joels et al., 2013). Recent studies suggest that corticosteroid can also rapidly influence synaptic activities via nongenomic mechanisms. It is proposed that release of corticosteroid from the HPA-axis orchestrates an array of crosstalk within the limbic areas, such as amygdala, prefrontal cortex (PFC), and hippocampus, to facilitate behavioral adaptation in response to stress (Groeneweg et al., 2011; Joels et al., 2013). Thus, it is thought that stress hormone has a complex impact on brain functions, largely depending on the exposure duration to stress and the associated levels of corticosterone being released. In agreement with this, experimental data have revealed the biphasic effects of stress on synaptic physiology and cognitive behaviors mediated by PFC, a critical brain region implicated in stress-related diseases (Yuen et al., 2009, 2011, 2012; Popoli et al., 2011; McEwen and Morrison, 2013). This review will discuss current findings on the molecular basis underlying the regulation of synaptic physiology and cognitive functions by corticosteroid stress hormones.

## Stress Effects on Cognitive Functions

Human studies support the procognitive effect produced by acute stress. Imaging of functional magnetic resonance imaging (fMRI) shows that acute stress enhances PFC signals during the performance of working memory tasks (Porcelli et al., 2008). Oral administration of hydrocortisone improves working memory performance and elevates dorsolateral PFC activity in humans (Henckens et al., 2011). Moreover, using pharmacological tools to decrease cortisol levels significantly impairs the PFC-dependent cognitive performance, which is restored by hydrocortisone replacement (Lupien et al., 2002a, 2002b). Correlating to human studies, acute stress significantly improves the performance of working memory in young rats (Yuen et al., 2009, 2011). Interestingly, acute stress can also enhance the later ability to acquire new associative memory. Animals exposed to the inescapable tail shock stress have the facilitated classical conditioning of eyeblink responses (Shors et al., 1992; Shors, 2006). Such ability is lost when peripheral adrenal medulla, the glucocorticoid-releasing organ, is removed (Beylin and Shors, 2003).

In addition to the procognitive effect of acute stress, some human and animal studies also show that acute, uncontrollable stress impairs PFC-mediated cognitive functions (Arnsten, 2009; Hermans et al., 2014; Arnsten et al., 2015). For instance, fMRI studies unveil that healthy participants who are exposed to an experimentally induced acute psychological stress show significantly impaired working memory-related activity in the dorsolateral PFC (Qin et al., 2009). Exposing monkeys to continuous loud noise stress for 30 minutes impairs delayed-response performance in the spatial working memory task, a PFC-mediated cognitive function (Arnsten and Goldman-Rakic, 1998). Rats exposed to acute (15 minute) tail-pinch stress have less accurate recall on a PFC-dependent cognitive task that is sensitive to working memory deficits, and

the stress-induced errors are reversed by blockade of glucocorticoid receptors in the medial PFC (Butts et al., 2011). The impairing effect of acute stress often occurs at the very early stage, which is likely due to the fast increase of the concentration of catecholamines, such as norepinephrine and dopamine, in the frontal cortical region (Abercrombie et al., 1989; Finlay et al., 1995; Murphy et al., 1996; Marsteller et al., 2002; Pascucci et al., 2007). High levels of noradrenergic and dopaminergic receptor activation trigger intracellular signaling pathways, which reduces the excitability of PFC neurons, leading to the weakening of PFC function (Birnbaum et al., 2004; Vijayraghavan et al., 2007; Gamo et al., 2015).

To integrate the intricate stress responses, the factor of timing with respect to stressor onset needs to be considered (Hermans et al., 2014). Human studies have found that the PFC activity related to an executive control task decreases shortly following stress induction (Qin et al., 2009) but enhances at a 240-minute delay (Henckens et al., 2011). It has been proposed that the rapid changes in catecholamines / glucocorticoids ratios in response to acute stress may determine the diverse effects on cognitive processes (Hermans et al., 2014). Right after acute stress, the increased catecholamines promote vigilance at the cost of an executive control network. After stress subsides, the increased glucocorticoids enhance higher-order cognitive processes for long-term survival (Hermans et al., 2014).

Importantly, the outcome of stress appears to be determined by the duration and severity of the stressor (de Kloet et al., 2005; Joels M, 2008). Contrary to acute stress, repeated or prolonged unpredictable stress causes the prominent deficit in working memory and recognition memory (Yuen et al., 2012), depression-like phenotypes, including increased immobility in tail suspension test, and increased latency to feed in novelty-suppressed feeding (Seo et al., 2016). In humans, impairment of cognitive function also correlates to the duration of stressor. Imaging studies show that 1-month exposure to psychosocial stressor produces a long-standing but reversible impairment of the PFC-dependent attention shifting task (Liston et al., 2009). However, cumulative life stressful events, such as death or chronic illness of a family member, cause a prominent volume loss in medial PFC and irreversible deficit in spatial working memory (Ansell et al., 2012; Hanson et al., 2012). Taken together, these results suggest that stress exerts complex effects on PFC-mediated functions presumably by linking to divergent molecular pathways.

## Stress Effects on Synaptic Physiology

### *The Impact of Acute Stress on Glutamatergic Transmission*

Introducing a short period of stressful stimuli to animals, such as forced swim, foot shock, or restraint, produces significantly enhanced glutamatergic transmission in PFC circuitry. This increased transmission is shown to be related to the enhancement of readily releasable pool of glutamate vesicles via a nongenomic mechanism mediated by membrane receptors (Moghaddam, 1993; Bagley and Moghaddam, 1997; Popoli et al., 2011; Treccani et al., 2014). Such stress-induced increase

in glutamate release is caused by the accumulation of presynaptic SNARE complexes in synaptic membranes of PFC neurons (Musazzi et al., 2010; Tardito et al., 2010). Moreover, acute footshock stress increases spine density and excitatory synapses and induces dendritic remodeling in medial PFC, which can be partially blocked by chronic treatment with the antidepressant desipramine (Nava et al., 2014, 2017a; Musazzi et al., 2015). Interestingly, recent study reveals that although both acute stress and in vitro application of corticosterone increase the size of readily releasable pool of synaptic vesicles in PFC, only acute stress enhances depolarization-evoked release of glutamate in PFC, which is positively correlated with phosphorylated synapsin I in PFC synaptic membranes (Musazzi et al., 2010; Treccani et al., 2014).

Besides presynaptic increase of glutamate release, acute stress also produces postsynaptic modification at PFC synapses. Patch-clamp recordings in PFC pyramidal neurons taken from acutely stressed animals shows a delayed and long-lasting potentiation of both NMDAR- and AMPAR-mediated synaptic currents (Yuen et al., 2009, 2011). The delayed time course suggests a genomic mechanism. Serum- and glucocorticoid-inducible kinases (SGKs), an immediate early gene activated by stress hormone, is shown to be involved in the stress-mediated glutamate receptor trafficking in PFC neurons (Yuen et al., 2012). Activation of SGK enhances the activity of Rab4, a small GTPase mediating the trafficking of glutamate receptors from early endosomes to plasma membrane (Liu et al., 2010; Popoli et al., 2011; Yuen et al., 2012). SGK is proposed to be one of the critical regulators of learning and memory. Transfecting SGK facilitates spatial memory performance in rats, and elevated SGK expression levels are found in hippocampus of rats with faster learning (Tsai et al., 2002). On the other hand, reduced SGK expression is found in postmortem brains of PTSD patients, and inhibition of SGK in rat PFC produces helplessness- and anhedonic-like phenotypes (Licznarski et al., 2015).

Posttranslational modification of glutamate receptors may also play a role in the acute footshock stress-induced, time-dependent modification of AMPAR and NMDAR subunits at PFC (Bonini et al., 2016). Phosphorylation of GluR1 at Ser 845, which is linked to the increased AMPAR channel open probability (Wangs et al., 2005), is elevated immediately after stress (Bonini et al., 2016). At 2 hours after start of stress, NR1 and NR2A subunits in postsynaptic spines are markedly upregulated, and phosphorylation of GluR2 at Ser 880, which is involved in promoting AMPAR internalization (Scannevin et al., 2000), is elevated (Bonini et al., 2016). These changes may underlie the early enhancement of AMPAR-mediated currents, followed by the potentiation of NMDAR-mediated currents in animals exposed to footshock stress.

The role of acute stress in glutamate receptor trafficking is supported by additional studies. A single (60 minute) restraint stress enhances the expression of Arc, an activity-dependent cytoskeletal-associated protein involved in AMPAR endocytosis (Fumagalli et al., 2011). Interference of adhesion molecules that anchor glutamate receptors at the synaptic surface abolishes the acute stress-induced enhancement of GluR2 membrane trafficking and memory facilitation (Conboy and Sandi, 2010). In addition, acute footshock stress induces both rapid and sustained alterations of the expression of key genes involved in synaptic plasticity and spine structure, such as *Homer*, *Shank*, *Spinophilin*, *Rac1*, and downstream target genes *Limk1*, *Cofilin1*, and *Rock1* (Nava et al., 2017b). Overall, acute stress facilitates postsynaptic signaling molecules or adhesion/cytoskeleton networks that support the synaptic trafficking of glutamate receptors.

### The Impact of Chronic Stress on Glutamatergic Transmission

Impairment of cognitive flexibility in chronically stressed individuals has been associated with the suppression of mPFC activity (Liston et al., 2006). A 21-day restraint stress produces impaired dendritic branching, atrophy, and spine loss in PFC pyramidal neurons (Radley et al., 2006; Popoli et al., 2011; Musazzi et al., 2015), and such structural reorganization is found to be reversible after 3-week cessation of stress (Radley et al., 2005). Having a prior chronic exposure to corticosterone causes a reduction of NR2B and GluR2/3 subunit expression in ventromedial PFC (Gourley et al., 2009). Consistently, a prominent loss of GluR1 and NR1 subunit expression has been found in PFC pyramidal neurons from repeatedly stressed animals (Yuen et al., 2012). Such changes lead to a long-lasting depression of both NMDAR- and AMPAR-mediated currents in PFC.

The loss of glutamate receptor expression in PFC of repeatedly stressed animals is attributable to the increased ubiquitin/proteasome-mediated degradation, which is controlled by E3 ubiquitin ligases Nedd4 and Fbx2. Inhibition of proteasomes or knockdown of Nedd4 and Fbx2 in PFC abolishes the loss of glutamate receptors by repeated stress (Yuen et al., 2012). The transcription of Nedd4 is upregulated by repeated stress via an epigenetic mechanism involving the elevated histone deacetylase 2 (HDAC2). HDAC2 inhibitors prevent the impairment of glutamate receptors and excitatory transmission in PFC of chronically stressed animals (Wei et al., 2016).

Chronic unpredictable stress has also been found to induce extracellular glutamate accumulation and the enhanced NR2B-mediated extrasynaptic response, which is associated with the increased interaction of Death-associated protein kinase 1 (DAPK1) with NMDARs (Li et al., 2017a). Uncoupling of the DAPK-NR2B complex, knockdown of DAPK, and pharmacological blockade of NR2B all produce the rapid antidepressant effects in chronically stressed animals (Li et al., 2017a).

### Additional Molecular Players Involved in Stress Effects

A multifunctional protein highly enriched in layer II-III PFC pyramidal neurons, p11, has been found to play an important role in stress-induced depression (Seo et al., 2016). p11 interacts with 5-HT receptors, ion channels, enzymes, and chromatin-remodeling factors and is critically involved in depression-related behaviors and/or antidepressant actions (Svenningsson et al., 2013). Chronic restraint stress induces the selective loss of p11 in PFC. Viral expression of p11 in PFC rescues the stress-induced suppression of glutamatergic transmission and depression-like behaviors (Seo et al., 2016).

Neurotrophic factors, such as brain derived trophic factor (BDNF), vascular endothelial growth factor, fibroblast growth factor 2, and insulin-like growth factor 1 (IGF1) are suggested as one of the important players in synaptic plasticity induced by long-term stress (Hill et al., 2011; Musazzi et al., 2011; Duman et al., 2016). Individuals carrying the Val66met allele of the BDNF gene have increased vulnerability to stress and antidepressant responses (Yu et al., 2012; Nava et al., 2014, 2015). Such a polymorphism shows the decreased activity-dependent BDNF secretion (Egan et al., 2003). BDNF expression is suppressed in animals exposed to various stress paradigms (Vaidya et al., 1997; Treccani et al., 2014; Musazzi et al., 2016). Application of corticosterone decreases BDNF expression (Schaaf et al., 1998) but increases BDNF in animals undergoing adrenalectomy (Chao et al., 1998). BDNF overexpression increases dendritic arborization in hippocampal neurons (Tolwani et al., 2002), blocks

chronic stress-induced hippocampal atrophy, and improves depression-like behaviors (Govindarajan et al., 2006). Chronic stress is also known for suppressing neurogenesis, a process promoting proliferation and survival of newborn neurons in adult brain (Duman, 2004). Antidepressant treatment reverses the stress-induced downregulation of neurogenesis (Duman, 2004), which is likely through BDNF-mediated tyrosine kinase-regulated signal transduction (Duman and Monteggia, 2006).

Many other molecular targets of stress are also involved in synaptic alteration. Animals exposed to chronic unpredictable stress have the decreased expression of Neuritin, a synaptic activity-dependent gene, which is reversed by antidepressant treatment. Viral knockdown of Neuritin prevents the stress-induced atrophy of dendrites and spines and the depression-like behaviors (Son et al., 2012).

Another stress-activated molecule, mTORC (also known as mammalian target of rapamycin complex), also receives much attention in the field. The mTORC signaling is found to be suppressed by cellular stress (Corradetti et al., 2005). Decreased levels of mTORC are reported in postmortem brains of individuals with stress-related mood disorders (Jernigan et al., 2011), whereas the rapid-acting antidepressant ketamine increases mTORC signaling in rat PFC (Li et al., 2010). REDD1 (regulated in development and DNA damage responses-1) is an endogenous inhibitor of mTOR. Enhanced expression of REDD1, together with inhibition of downstream cascades of mTOR, are concomitantly found in the PFC of animals exposed to 21-day unpredictable stress (Ota et al., 2014). Animals with REDD1 knockdown have greater resilience to the chronic stress-induced spine shrinkage and AMPAR current reduction (Ota et al., 2014). Moreover, REDD1 level is found to be significantly elevated in postpartum depressed human brains and is thought to play a key role in the stress-induced depressive phenotypes (Ota et al., 2014).

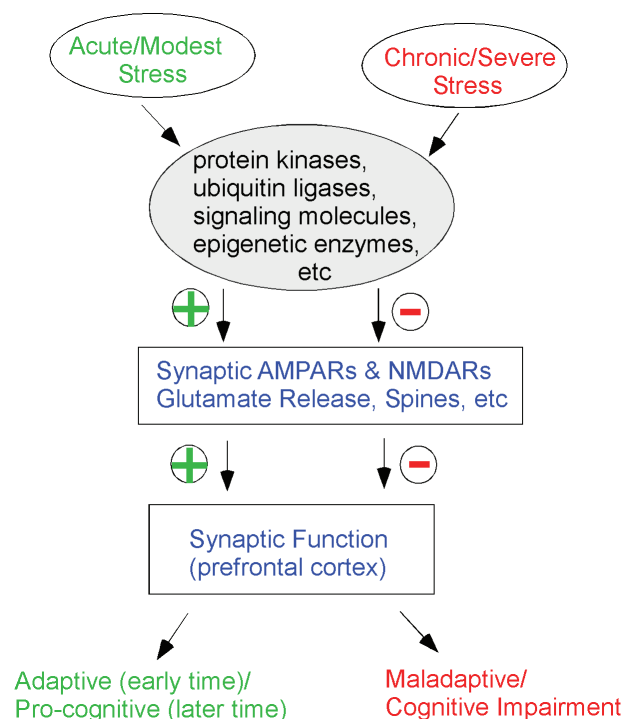
Recent studies propose a new concept that inflammatory cytokine can be a central mediator linking stress to psychiatric disorders and other systemic diseases (Musazzi et al., 2011; Iwata et al., 2013; Duman et al., 2016). Supporting this theory, depressed patients show elevated proinflammatory cytokines, such as tumor necrosis factor and interleukin 1 $\beta$ , which are reversed by antidepressant treatment (Pascucci et al., 2007; Arnsten, 2009; Dowlati et al., 2010). Pharmacological blockade or genetic knockout of caspase-1, an interleukin 1 $\beta$ -converting enzyme, prevents the chronic restraint stress-induced, depressive-like phenotypes in mice by stabilizing surface AMPARs (Li et al., 2017b). Interestingly, levels of cytokine also demonstrate a biphasic relationship with synaptic transmission. It is suggested that intact glutamatergic transmission requires a moderate level of inflammatory molecules. A low level of cytokine promotes new AMPAR insertion and glutamate release from astrocyte in an activity-dependent synaptic modification (Santello and Volterra, 2012). However, "too much" inflammatory cytokine leads to impairment of long-term potentiation and synaptic loss (Finlay et al., 1995; Boulanger, 2009; Arnsten et al., 2015). Blocking the activation of cytokine reverses anhedonic phenotypes induced by chronic unpredictable stress (Iwata et al., 2016).

### Epigenetic Factors in Stress Effects

It has been a fascinating question whether stressful experience or its phenotype can be transmitted across generations. If so, what are the molecular substrates to determine vulnerability or resilience to stress? It is shown that chronic maternal separation alters the profile of DNA methylation at particular genes in the sperm of stressed animals (Franklin et al., 2010)

and alters the HPA stress responsiveness of offspring (Rodgers et al., 2013). Interestingly, injecting sperm RNAs from stressed males into wild-type oocytes creates offspring with behavioral and metabolic phenotypes similar to the stressed father (Gapp et al., 2014). Recent studies have identified genes that contribute to stress susceptibility, including the ones within the HPA axis (Polanczyk et al., 2009), serotonin receptors (Yu et al., 2012; Nava et al., 2014, 2015), and neuropeptide Y (Finlay et al., 1995; Marsteller et al., 2002; Domschke et al., 2010; Liu et al., 2010).

Emerging evidence indicates that aberrant gene transcription via chromatin remodeling or histone modifications contributes to the stress-induced maladaptive changes, including neuronal plasticity, synaptic neurotransmission, as well as cognitive processes. In response to chronic stress, histone acetylation level is robustly changed in different brain regions. In nucleus accumbens, decreased HDAC2 and HDAC5 expression is observed in depressed animals or humans (Renthal et al., 2007; Covington et al., 2009). In the hippocampus of stressed animals, global acety-H3K14 shows a transient increase, followed by a persistent decrease, which is associated with changes in BDNF gene expression (Tsankova et al., 2006; Covington et al., 2011). In amygdala, H3K14 acetylation is found to be transiently increased after social defeat stress, while HDAC5 is significantly decreased after unpredictable stress (Covington et al., 2011; Sterrenburg et al., 2011). Repeated stress increases HDAC2 in rat PFC, which causes the epigenetic alteration of Nedd4, an E3



**Figure 1.** A diagram illustrating the complex effects of stress on prefrontal cortex (PFC) synaptic physiology and PFC-mediated functions. Acute/modest stress or chronic/severe stress induces divergent changes on protein kinases, ubiquitin ligases, signaling molecules, and epigenetic enzymes, which leads to the convergent and opposite alterations of postsynaptic glutamate receptors, presynaptic glutamate release, and dendritic spine structure. Consequently, glutamatergic synaptic function in prefrontal cortex is bi-directionally changed, resulting in adaptive or maladaptive effects on cognitive processes. In response to acute stress, executive control can be compromised at the early time point as a result of the promoted emotional reactivity for short-term adaptation, while higher-order cognitive processes are enhanced at later time points for long-term survival.

ubiquitin ligase for AMPAR degradation, leading to the impairment of AMPAR expression and cognitive function (Wei et al., 2016). In addition, various HDAC inhibitors are implicated in antidepressant responses in stressed animals (Covington et al., 2009; Sun et al., 2013; Bagot et al., 2014; Wei et al., 2016).

In addition to histone acetylation, DNA methylation is found to be altered in stressed animals. Animals with better maternal care are found to have decreased DNA methylation of the glucocorticoid receptor gene, leading to the increased expression of the receptors and more resilient stress response in adult (Weaver et al., 2005). Such resilience can be reversed by introducing hypermethylation of glucocorticoid receptors in adult rats (Marsteller et al., 2002; Tsai et al., 2002; Weaver et al., 2005; Liu et al., 2010). Genes controlling HPA axis adaptation have also been found to contribute to stress resilience. The expression of Corticotropin-Releasing Hormone is elevated in the hypothalamus of animals that develop social avoidance after exposure to chronic social defeat stress (Elliott et al., 2010). However, in the subset of animals that do not show stress-induced social avoidance, their Corticotropin-Releasing Hormone gene is hypermethylated. Environmental enrichment reduces basal ACTH and stress responses (Moncek et al., 2004), suggesting a possible link among epigenetic, genetic, and environmental factors contributing to the HPA stress response.

In conclusion, recent studies introduce the concept of biphasic stress responses in cognitive processes mediated by prefrontal cortex, through modulating molecular substrates at glutamatergic synapses (Figure 1). Changes in presynaptic glutamate release, postsynaptic glutamate receptor trafficking and expression, spine structure and cytoskeleton network, and epigenetic control of plasticity genes all contribute to the complex effects of stress. Despite the richness of information in this field, there are still key questions waiting to be answered. For example, how is the adaptive response to short-term modest stress switched to the maladaptive response to long-term severe stress? Why does the vulnerability to stress differ a lot among individuals? How much translational value do the results from animal studies have? Understanding the mechanisms that regulate glutamatergic synaptic function in PFC may shed light on identifying pathophysiology and novel pharmacological intervention for stress-related psychiatric disorders.

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## Statement of Interest

None.

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