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The Fragile Brain: Stress Vulnerability, Negative Affect and GABAergic Neurocircuits in Psychosis

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Persons with schizophrenia exhibit sensitivity to stress and negative affect (NA), both strongly correlated with poor functional outcome. This theoretical review suggests that NA reflects a "fragile brain," ie, vulnerable to stress, including events not experienced as stressful by healthy individuals. Based on postmortem evidence of altered gamma-aminobutyric acid (GABA) function in parvalbumin positive interneurons (PVI), animal models of PVI abnormalities and neuroimaging data with GABAergic challenge, it is suggested that GABAergic disruptions weaken cortical regions, which leads to stress vulnerability and excessive NA. Neurocircuits that respond to stressful and salient environmental stimuli, such as the hypothalamic-pituitary-adrenal axis and the amygdala, are highly dysregulated in schizophrenia, exhibiting hypo- and hyper-activity. PVI abnormalities in lateral prefrontal cortex and hippocampus have been hypothesized to affect cognitive function and positive symptoms, respectively; in the medial frontal cortex (dorsal anterior cingulate cortex and dorsal medial prefrontal cortex), these abnormalities may lead to vulnerability to stress, NA and dysregulation of stress responsive systems. Given that postmortem PVI disruptions have been identified in other conditions, such as bipolar disorder and autism, stress vulnerability may reflect a transdiagnostic dimension of psychopathology.

Key words: schizophrenia/emotion/anterior cingulate cortex/benzodiazepine/amygdala/HPA axis

Introduction

Clinicians working with schizophrenia inevitably notice that their patients often exhibit emotional fragility and sensitivity to minor stresses. These negative affective states appear in contrast to the emotional deficits first noted by Kraepelin and now incorporated into the concept of negative symptom or deficit schizophrenia.[1,2] Overactive emotions were also noted by Kraepelin, but particularly emphasized by Bleuler, who described "an over-sensitivity, so that the patients consciously and deliberately isolate themselves in order to avoid everything that may arouse affects."[3] In the mid-twentieth century, Meehl described the tendency toward negative affective states (aversive drift) as a fundamental process in the schizophrenia prodrome.[4] Deficits in emotional expression are a core phenomenological construct of negative symptoms,[5] but contemporary work recognizes that the absence of external expression of emotion sometimes conceals the presence of negative affective (NA) states.[6–8] The purpose of this review is to address this phenomenon of "stress sensitivity" in schizophrenia, focusing on the intrinsic vulnerability to stress and the tendency to exhibit NA in settings not ordinarily considered stressful. In what follows, we will review studies and put forth the hypothesis that inhibitory, gamma-aminobutyric acid (GABA)ergic interneurons play critical roles in determining stress vulnerability and the tendency to experience NA in schizophrenia.

Vulnerability and the Tendency to Negative Affect

Stress-Vulnerability in Schizophrenia

The stress-vulnerability, or "stress-diathesis," framework was first formulated for schizophrenia over 40 years ago.[9,10] Biologically, stress is usually conceptualized as an "allostatic load," where "allostasis" refers to the adaptive process of maintaining stable autonomic, immune, and hypothalamic-pituitary-adrenal (HPA) axis function in response to environmental challenges.[11,12] Schizophrenia patients are highly sensitive to stress,[13–22] and this review will build upon this prior work. Our focus will be on the *vulnerability itself*, which we define as the tendency to experience NA, and which we attribute to a low threshold for what is experienced as stressful.

While the stress-vulnerability framework has been very useful, it may place an undue emphasis on

antecedent events as potential triggers of the disorder. It is important to distinguish schizophrenia from post-traumatic stress disorder (PTSD), although there is comorbidity of the 2 diagnoses,[23] and some evidence suggests that psychosis can emerge secondary to PTSD.[24,25] However, careful examination of reported life events has shown that rather than having more adverse life events, schizophrenia patients experience events as more stressful than healthy subjects.[13,26] In clinical high risk groups, the evidence for stressful events preceding the new onset of psychosis is weak to nonexistent, according to a recent review.[27] On the other hand, in-the-moment studies of patient experience, using experience sampling methodologies (ESM), show that, through the course of the day, patients experience more negative emotions, and less positive emotions, than control subjects.[28–30] A recent meta-analysis found, relative to healthy controls, robust mean effect sizes of 0.84 for greater NA, and −0.75 for less positive affect.[28] Importantly, first-degree relatives of patients also show more NA,[31] suggesting that this tendency to NA may have a genetic component. Trait personality measures of persons with schizophrenia show high levels of NA, such as high scores on neuroticism scales, in addition to reduced levels of positive affectivity.[32–34] In a laboratory setting, schizophrenia patients tend to rate positive and neutral stimuli as being more negative, whereas they give largely equivalent ratings of negative stimuli as control subjects,[7] indicating an intact capacity to appraise stimuli,[6,35–39] although some have suggested that a subtype of patients may have a more negative experience of negative stimuli.[40] Taken together, the data demonstrate that persons with schizophrenia have more experience of NA than healthy persons.

The concept of a tendency to experience NA takes several forms. It is similar to Meehl's notion of "aversive drift"—"intensely negative affective states not clinically identifiable as variants of the commonly recognized aversive emotions."[41] A patient account of living with schizophrenia illustrates the emergence of NA through the course of daily life, wherein vulnerability can be seen as a limited capacity to engage with the environment:

> People like my husband who are rich with mental health are blessed with 100 pennies, while I, having a thought disorder, only get 20 pennies…. Before I commit myself to almost any sort of action, I often silently calculate: how much will this activity drain me? Every sundry task costs…. If I am not careful, I can spend all my pennies by 12 noon…. The world turns dark and threatening, and all my earthly delights and good fortune are forgotten.[42]

This writer, in noting that "Every sundry task costs," captures an alternative way to think about stress vulnerability—that it reflects a reduced capacity for engaging with the environment. With reduced capacity, the threshold for what makes an event stressful is lowered. Why NA emerges when a limited processing capacity is exceeded is a critical question for future research, which this review seeks to stimulate (table 1).

A Model of Vulnerability and Negative Affect

Our conceptual model is depicted in figure 1. Stress vulnerability, or simply "vulnerability," is conceptualized as a latent construct, driving NA, itself a latent construct comprised of the measurable phenotypes of anxiety, depressive mood, and general distress. NA might arise in the absence of external triggers, although it is difficult to distinguish spontaneously arising NA from NA triggered by an event. Some events are stressful enough that they cause NA, regardless of an underlying vulnerability, whereas other events, eg, involving novelty or requiring adaptation, strain a limited capacity to process information, and lead to NA, moderated by vulnerability. Not all NA reflects vulnerability, especially in physical conditions (somatic pain, drug side effects). Current environmental threats, such as poverty and discrimination, may directly cause NA, and this causal relationship may be moderated by the vulnerability.

The model also includes etiological factors associated with schizophrenia, which may cause deficits in GABAergic interneurons (discussed below). Environmental stresses in early life and adolescence, such as social deprivation, urbanicity, and toxin exposures,[19,21,43,44] as well as obstetric complications,[44–46] have been linked to schizophrenia and the risk of developing a psychosis. Among environmental stresses, childhood trauma stands out as a risk factor, occurring in up to one-third of patients with schizophrenia,[47–50] and childhood trauma has been linked to NA and emotional problems in adolescence and adulthood.[51,52] Some stresses may be chronic and more subtle, but persistent enough to wear down adaptive mechanisms (inducing vulnerability) and directly causing negative affect.[53] Genetics is another possible etiological factor. Polygenic risk scores for schizophrenia are associated with NA in adolescence and adulthood[54–56]; and genome-wide association studies[57] and analysis of copy number variants[58] have strongly implicated GABAergic signaling in schizophrenia. It is beyond the scope of this review to go into each one of these potential causative factors, and we do not mean to imply that these factors do not act on the clinical phenotype through other pathways, leading to symptoms besides NA. Our emphasis here is on NA.

Specifically, we hypothesize that this vulnerability is linked to abnormalities in GABAergic, parvalbumin positive interneurons (PVI), in conjunction with their relationship to excitatory pyramidal cells. It has been suggested that damage to these vulnerable, fast-spiking interneurons is a final common pathway of many mental illnesses besides schizophrenia, including bipolar disorder, autism, and depression, mediated by converging influences of

Table 1. Questions for Future Research

Questions	Possible Methods of Investigation
1) If stress vulnerability can be thought of as reduced capacity to handle events, why does NA emerge when this capacity is exceeded? Are there are other signs that a limited capacity has been exceeded, besides NA? What are the neurocircuits which carry this load?	Animal models, neuroimaging studies, stress and emotion challenges, experience sampling methodologies, computational modeling
2) What are the developmentally sensitive periods for the emergence of NA associated with the development of psychosis?	Longitudinal studies including critical developmental periods, animal models
3) What is the relationship between vulnerability and cognition? Between vulnerability and negative symptoms?	Clinical phenotyping and analytics, eg, network analysis, structural equation modeling, causal modeling, etc.
4) If cognitive function is improved, can NA be properly regulated?	Cognitive behavior therapy for psychosis, cognitive training, pharmacologic cognitive enhancers
5) How can we separate NA related to a GABAergic (PVI) deficit from other causes of NA?	Multimodal neuroimaging and EEG with pharmacologic challenge; animal models
6) How much of the vulnerability in schizophrenia is shared across other disorders?	Transdiagnostic studies (including postmortem samples), genetic markers (polygenic risk scores)

peri-natal stress and inflammation, all triggering oxidative stress.[59] Here, our model becomes trans-diagnostic, as implied in the previous paragraph, where risk factors for schizophrenia, such as early life stress, are also risk factors for other psychiatric disorders.[51,52] In addition to their vulnerability to a variety of insults, PVI neurons mature later in life,[60] and they are highly sensitive to stress early in life,[61] which might be one explanation for developmental periods when traumatic events can have more of an adverse impact on emotion regulation in adulthood.[62,63]

For the purposes of this review, we will limit our focus to schizophrenia. Many of the studies we cite include schizoaffective patients, but there has been little attempt to differentiate NA in schizoaffective disorder and schizophrenia, aside of the obvious higher incidence of NA (depressive symptoms) in schizoaffective disorder.[64] Although we see the proposed GABAergic mechanisms of vulnerability and NA as transdiagnostic, most of the relevant research has occurred in schizophrenia; hence, our focus.

Negative Affect and Schizophrenia Symptoms

A diagnosis of schizophrenia does not require the presence of anxiety or depressive symptoms, but NA is frequently present. Factor analytic studies of clinician-administered rating scales, such as the Positive and Negative Symptom Scale (PANSS), consistently show the emergence of a depression/anxiety factor, along with positive symptoms, negative symptoms, disorganization, and excitement.[65–67] Depression occurs in 30%–50% of schizophrenia patients,[68,69] and social phobia in 13%–36% of schizophrenia cases,[70–72] with as many as 60% of patients experiencing some form of social anxiety.[73] NA is associated with poor social functioning and poor quality of life, after controlling for positive and negative symptoms,[32,64,74,75] suggesting that it is an important target for interventions.

In our model, we indicate that this GABAergic vulnerability is also linked to cognitive dysfunction and positive symptoms (hallucinations and delusions). While NA appears as an independent component of the clinical phenotype, it is also true that positive symptoms, eg, persecutory delusions causing fear, can directly contribute to NA. The causality may go both ways, as NA/vulnerability could also exacerbate positive symptoms. Stressful events have been linked with variation in positive symptoms,[13,76] although sample sizes have been small and most studies have been cross-sectional. Another possibility is that PVI deficits may directly lead to positive symptoms, as suggested by animal models and theoretical considerations, which we discuss below.

The question of to what degree NA might reflect cognitive deficits and a failure to inhibit NA remains an unsettled area of study. Limited work has been done in this area. An inverse relationship between neurocognition and stress sensitivity was reported in one study,[77] whereas another group found that poor memory performance was directly related to more NA.[78] Studies have generally found that NA is an independent predictor of poor functional outcome, after controlling for neurocogni tion,[64,75,79,80] but this does not preclude that cognition might interact with NA, as some have found.[79] Indeed, as we suggest, PVI dysfunction may be a "third variable" that could also cause the association between impaired cognition and NA.

Negative symptoms have a more complicated relationship with NA, which is not yet worked out sufficiently to be included in figure 1. As mentioned above, factor analytic studies have pulled out NA measures distinct from negative symptoms.[65–67] A recent categorial formulation distinguished a distress subtype, distinct from the deficit (enduring negative symptom) subtype in chronic schizophrenia patients,[81] and a network analysis of negative symptoms found an inverse relationship with NA.[82] Using continuous measures, others have found higher negative

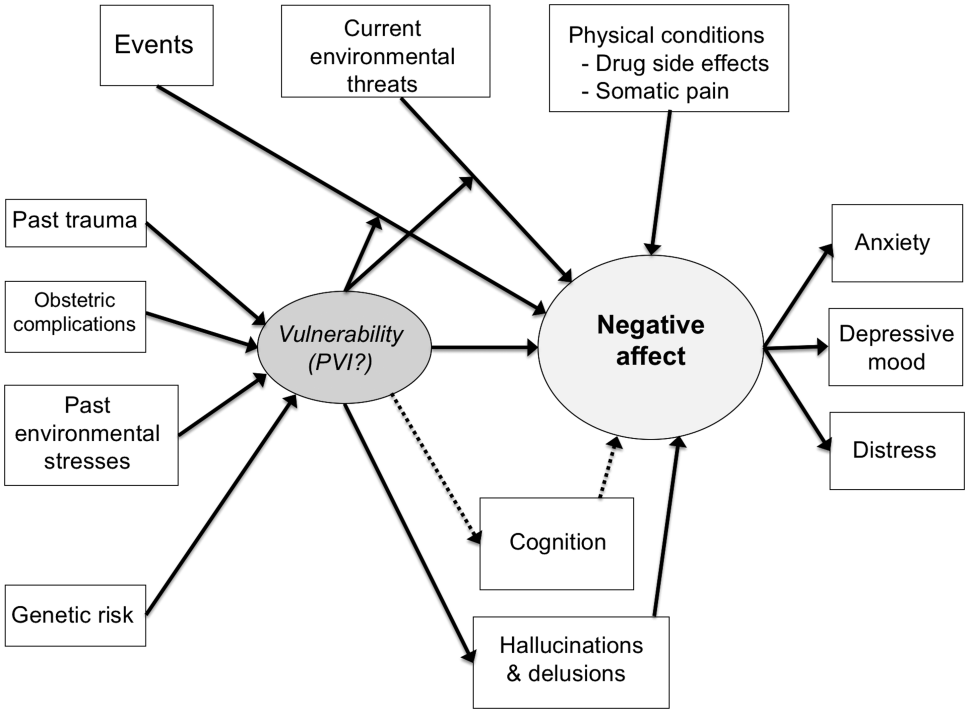

Fig. 1. Relationship between negative affect (NA) and stress vulnerability. Solid lines indicate positive relationships, while dotted lines indicate negative relationships. Vulnerability moderates the influence of events and environmental threats to produce NA. An event, which could be a benign social interaction, could turn into a stressful event through this moderation. Cognition and hallucinations/delusions are also posited in a causal relationship with the underlying GABAergic mechanism, but through different neurocircuitry than NA (figure 2). PVI, parvalbumin positive interneurons.

symptoms associated with reduced NA[29,83] and less reactivity to negative stimuli,[84,85] raising the intriguing possibility that affective flattening and amotivation might be an adaptation to NA. On the other hand, studies of anhedonia have suggested that NA might contribute to anhedonia by reducing pleasure seeking behavior,[86] which could reflect a form of secondary negative symptoms, and that ratings of anhedonia, specifically anticipatory pleasure, is reduced by NA.[87,88] As with cognition, the relationship between NA and negative symptoms, primary and secondary, is an area for future research (table 1).

Evidence for Disruption of PVI in Schizophrenia

Postmortem Findings in GABAergic Systems

Postmortem studies have demonstrated abnormalities in GABAergic systems, prominently implicating PVI. Findings have included reductions in parvalbumin expression,[89] reductions in the synthetic enzyme for GABA, glutamic acid decarboxylase (GAD67),[90–93] alterations in pre- and postsynaptic terminals,[94] and reduction of the peri-neuronal nets surrounding PVI.[95] Reductions in mRNA levels of GABAergic-related neuropeptides have also been noted, such as neuropeptide Y, somatostatin, and cholecystokinin.[96] Abnormal PVI findings have been observed throughout the cortex[97–99] and hippocampus.[100,101] PVI cell counts are not reduced in the cortex,[102–104] while some have found reduced cell counts of PVI in hippocampus[105,106] and layers II/III of the anterior cingulate gyrus.[107] Evidence suggests that the changes are not due to extraneous factors, such as age, sex, or medication. Lastly, consistent with our transdiagnostic formulation, GAD67/PVI deficits have also been found in bipolar disorder,[92,108,109] although not as often in unipolar depression.[92,110]

The PVI findings have generated several pathophysiological models for schizophrenia. One type of fast-spiking PVI, the basket cells (PVBC), which synapse on the cell bodies of layer III, excitatory pyramidal cells, have been implicated in cortical gamma oscillations.[111–113] These oscillations are associated with integrative cortical functions such as attention and working memory in prefrontal cortex,[114–116] and they are abnormal in schizophrenia, suggesting a possible pathogenic mechanism of cognitive deficits.[117,118] One of the challenges in the field has been sorting out primary from secondary and compensatory changes. A primary deficit in PVBC might lead to disinhibition of pyramidal cell firing; alternatively, PVBC changes might be secondary. For example, a reduction in the dendritic spine density of pyramidal neurons could lead to reduced excitation, followed by compensatory adjustments to re-set the balance between excitation and inhibition, eg, reduced GAD67 to reduce GABA release, followed by increased postsynaptic GABA receptors

(GABAR).[91,119] GABAergic abnormalities have also been linked to hypofunction of the excitatory *N*-methyl-d-aspartic acid glutamate receptors (NMDAR), located on GABAergic interneurons.[120] For PVBC synapsing on hippocampal pyramidal cells, this could lead to hippocampal hyperactivity, increased dopaminergic activity and the positive symptoms of psychosis.[119,121] One intriguing idea around the re-setting of excitatory/inhibitory (E/I) balance is that the overall capacity of the system to process information would be reduced.[91] Importantly, the PVI findings have been noted across diverse areas of cortex, as well as subcortical structures, potentially implicating diverse behaviors (figure 2).

Animal Models of PVI Deficits

Prior theoretical work has focused on cognitive or positive symptoms, but there has been a surprising neglect of NA in the literature, in spite of the fact that animal models have implicated affect dysregulation. PVI disruption occurs in several developmental rodent models, including neonatal ventral hippocampal lesions,[122] maternal immune activation,[123–125] and prenatal infusion of methylazoxymethanol (MAM).[126,127] Reduced PVI immunoreactivity has been demonstrated in isolation-reared rats,[128] and in adult rats exposed to chronic stress through social isolation.[129,130] Mice exposed to immune activation in utero exhibit increased anxiety behaviors, as well as impaired set shifting behavior, but intact working memory.[123] MAM-treated rats exhibit heightened anxiety-related behavior as adults, increased firing of basolateral amygdala (BLA) neurons and larger increase in BLA theta power in response to conditioning stimuli, as well as reduced gamma-band response to a conditioned stimulus in the medial PFC.[131] Importantly, peripubertal administration of diazepam, which potentiates GABA receptors, reduces the anxiety, normalizes the BLA neuron firing rates and reduces the abnormally high theta power increase in the BLA seen by conditioning stimuli.[127] MAM-treated rats also exhibit increased spontaneous DA firing, which is also reduced by diazepam.

Another approach to modeling GABA dysfunction has directly targeted GAD1 (the enzyme which produces the GAD67 protein), and these models also show affective dysregulation. A knock-down mouse targeting PV+ neurons showed impaired fear extinction, along with impaired sensori-motor gating and increased novelty seeking.[132] With a different GAD1 knock-down mouse model, another group reported increased anxiety-related behavior in the open field test and light/dark box, as well as reduced effort-based behaviors, but intact spatial working memory and normal sensorimotor gating.[133] Overall, the behavioral phenotypes are not entirely consistent,[134,135] which may reflect different populations of GAD1-containing neurons besides PV+ interneurons, eg, cholecystokinin or somatostatin. While rodent models cannot be expected to capture all aspects of schizophrenia, it is notable that when PV+ neurons are targeted in a way that parallels the postmortem findings in the psychosis spectrum, an affective phenotype emerges.

Neurocircuits Implicated in Stress and Affect in Schizophrenia

Stress Response Systems in Schizophrenia

A considerable amount of research has focused on the physiological stress response in schizophrenia. Brain responses to stress-inducing stimuli activate several

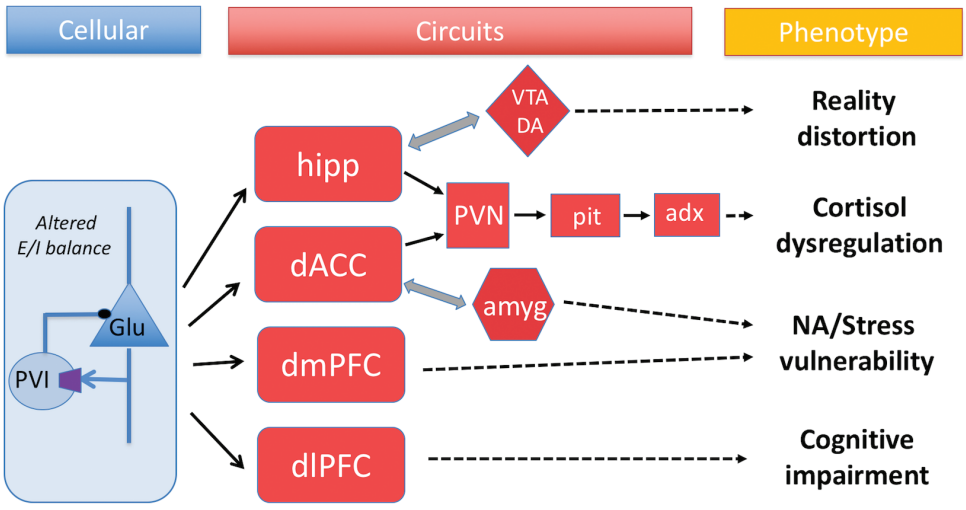

Fig. 2. Depending upon the cortical or subcortical structure affected, diverse phenotypic manifestations of GABAergic abnormalities in parvalbumin positive interneurons (PVI), working in concert with excitatory neurons to maintain proper excitatory/inhibitory (E/I) balance, may occur. hipp, hippocampus; VTA DA, ventral tegmental dopamine; PVN, paraventricular nucleus of hypothalamus; Pit, pituitary; Adx, adrenal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; dACC, dorsal anterior cingulate cortex; amyg, amygdala; ctx, cortex; Glu, glutamate. For color, see the figure online.

key systems in the brain, including the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal medullary system.[136,137] The latter is more associated with fast, short-term responses to stress, whereas the former has been the focus of most of the stress research in schizophrenia.[22,138–143] The HPA axis involves multiple levels of control and feedback, most easily studied by measuring the major secretagogue of the adrenal cortex, cortisol. Schizophrenia shows a complex picture of a dysregulated system. Baseline cortisol levels appear to be elevated in early schizophrenia, particularly in unmedicated cohorts, and possibly in at-risk subjects.[22,141–143] Studies of the cortisol awakening response (CAR) are fewer and show more inconsistencies, but a recent meta-analysis concluded that the CAR is blunted in schizophrenia, although not different in at-risk subjects.[139] Similarly, challenge studies with psychosocial stressors report a blunted cortisol response,[142] although a more recent review reached the opposite conclusion, noting similar levels of subjective stress responses in psychosocial challenge studies, except for patients early in the illness.[138] While cortisol measures have generally not shown consistent associations with symptoms and equivocal evidence for predicting conversion in high risk subjects,[22] a recent systematic review found somewhat consistent correlates with anxiety and stress-intolerance measures in at-risk subjects.[140] In general, the complexity of the findings likely reflects multiple, difficult-to-control factors, such as heterogeneity in patient samples, differences in measurement, variable medication status and the multiple upstream pathways that regulate the HPA axis.

Given these complexities, it is important to consider these upstream influences. The paraventricular nucleus (PVN) of the hypothalamus releases corticotrophin releasing hormone (CRH), which triggers the release of adrenocorticotropin releasing hormone in the pituitary, in turn triggering cortisol release by the adrenal cortex. This stress cascade is modulated by projections to the PVN from the hippocampus, amygdaloid nuclei, and medial frontal cortex,[137] all regions implicated in emotion.[144] Relatively little work in schizophrenia has addressed whether or not pathology exists at level of the hypothalamus, pituitary or adrenal gland, but an abundance of data demonstrates abnormalities in these limbic and cortical structures, as we discuss below.

Another neural system relevant for the stress response and centrally implicated in the pathophysiology of schizophrenia is dopamine. Contemporary accounts of the dopamine hypothesis increasingly suggest that dopamine dysregulation is a downstream consequence of dysregulation in other systems, eg, falsely signaling salient states and triggering dopamine release.[145,146] Stress elevates striatal dopamine release in animals[147] and humans,[148]and an impaired ability to regulate psychosocial stress has been suggested as one of the upstream triggers leading to hyper-dopaminergia and positive symptoms in schizophrenia.[149,150] One possible locus of this failure is the hippocampus, which is structurally and functionally abnormal in schizophrenia.[151–155] It is possible that hypercortisolemia causes the volume loss observed in the hippocampi of schizophrenia, leading to hippocampal dysfunction and dopamine dysregulation.[156] Animal models suggest that hippocampal GABA-glutamatergic circuits may send aberrant signals to midbrain dopaminergic neurons, leading to hyperactivity.[157,158] While such a mechanism could contribute to NA and positive symptoms, the fact that these 2 clinical phenomena are dissociable suggests that another mechanism might be implicated. For example, the medial frontal cortex, which also regulates the HPA axis,[137] may be another critical upstream structure responsible for stress vulnerability.

Affective Neurocircuits in Schizophrenia

Neuroimaging studies examining brain responses to salient emotional stimuli provide clues about neurocircuits relevant for stress vulnerability. A large body of work has implicated amygdala dysfunction in schizophrenia.[159–161] There is heterogeneity in the findings, and a pattern of dysregulation is more apparent than simple reductions or increases in reactivity. For example, while meta-analytic studies have repeatedly identified reduced activation to emotional face stimuli,[160,161] the amygdala may be hyperactive at baseline and activated by neutral stimuli that evoke less response from healthy subjects.[160] Measures of cerebral perfusion—resting activity not measurable by fMRI blood oxygenation level dependent (BOLD)—show increased amygdala activity in the absence of an emotional challenge.[162–164] The findings of reduced activity change with BOLD may reflect reduced dynamic range of measurable signal change, or a shift in the response of the amygdala to salient stimuli, in general.

The amygdala has strong connectivity with medial frontal structures, including the dorsal anterior cingulate cortex (dACC), rostral ACC, and ventromedial prefrontal cortex (vmPFC), as well as, to a lesser extent, the dorsal medial prefrontal cortex (dmPFC).[165,166] Several studies have found reduced connectivity in schizophrenia between the amygdala and medial frontal regions while processing emotional stimuli.[167–169] Neuroimaging studies show that medial frontal regions are associated with HPA axis activity,[170] regulate emotional responses and process social information, particularly around agency and theory of mind in the dmPFC.[144,171,172] Interestingly, when a GABA antagonist is infused in the prelimbic cortex (PL) of rats, homologous to the dACC in humans, the rats respond to cues not previously paired with an aversive stimulus as if those cues predicted the aversive stimulus.[173] PL is also associated with turning down the HPA axis, and disrupted PL is associated with HPA axis dysregulation.[137] Given that NA very frequently emerges in social situations,

impaired medial frontal-amygdala connectivity could be one of the neurocircuit substrates of stress vulnerability, including dysregulation of the HPA axis.

It is noteworthy that both the HPA axis and the amygdala, neural systems that are tuned to detect salient stimuli and mobilize appropriate responses, have been observed as both hypo- and hyper-responsive in schizophrenia. We have suggested this reflects not primary deficits in these systems, but instead, dysregulation by the upstream, cortical and subcortical circuitry that regulate them, particularly in the mPFC and dACC (figure 2). A meta-analysis of emotion perception in schizophrenia showed reduced activation during emotion perception in the dACC, medial prefrontal cortex (mPFC), visual processing areas, dorsolateral prefrontal cortex (dlPFC), thalamus and caudate, along with increased activation in posterior regions not typically activated by emotion probes.[161] A meta-analytic study of theory of mind showed hypoactivation in the mPFC,[174] and 2 large meta-analyses have identified prominent structural deficits in mPFC and dACC.[175,176] Thus, these cortical regions stand out as possible loci of dysfunction involved in vulnerability.

Functional Studies of GABA in Schizophrenia

A dearth of in vivo studies of GABA function in humans has limited the understanding of GABAergic activity and behavior. Neuroimaging studies of GABAR binding and GABA levels have been equivocal and difficult to interpret, and a full discussion of these area is beyond the scope of the present review (see refs.[177,178]).

Pharmacologic challenge studies can provide insight into dynamic GABA function.[178,179] For instance, we gave schizophrenia patients and healthy comparison subjects intravenous bolus infusions of lorazepam (LRZ) and saline (SAL) in a within-subjects, cross-over design to probe GABAergic activity with fMRI while subjects viewed salient emotional stimuli.[178] In addition to an expected effect of reduced BOLD signal in occipital cortex, we found group by drug interactions in the fusiform gyrus, right superior frontal gyrus and dmPFC. Schizophrenia patients showed an *increased BOLD signal* to LRZ challenge, rather than the decreased signal exhibited by the comparison group, and more positive BOLD change after LRZ directly associated with greater NA. By potentiating GABA receptors with LRZ, the challenge paradigm revealed dysregulated dynamics of GABA receptors and the excitatory pyramidal cells with which they interact in the cortex, a dysregulation that might reflect the PVI disruptions found in postmortem data. Of course, the relatively crude BOLD signal does not enable the cellular resolution necessary to test this hypothesis, but it does show an abnormality consistent with these postmortem findings. It also shows the link between trait-level NA and GABA dynamics. Localization of this effect to dmPFC and occipital cortex is consistent with neuroimaging findings of abnormal emotion processing in schizophrenia.[161,164,180–182]

Treatment Implications

Treatment With GABAergic Agents

Suggestions to use GABAergic drugs to treat schizophrenia are not new.[183–187] Benzodiazepines (BDZ) and valproic acid, which both potentiate GABA transmission, have been used clinically, usually as adjunctive agents to manage NA and agitation.[188–190] Although a recent Cochrane review found no support for BDZ as effective augmentation agents in schizophrenia,[191,192] the level of evidence was generally poor, and the authors could not conclude that BDZ did not help. In fact, they concluded there was support for the use of BDZ for acute agitation and anxiety in schizophrenia. Anxiety is a form of NA, and the fact that BDZ have utility in the treatment of schizophrenia, at all, is an important clue about underlying mechanisms. While BDZ are generally not regarded as antipsychotics, diazepam has been shown to reduce psychotic relapse in schizophrenia patients in a randomized clinical trial.[193] Iomazenil, a partial inverse agonist of the benzodiazepine receptor, increases psychotic symptoms in schizophrenia patients,[194] further implicating GABA mechanisms.

An intriguing clinical linkage between GABA and therapeutics can be seen in catatonic states, which often respond dramatically and rapidly to benzodiazepines.[195,196] Catatonia patients often show very strong NA, sometimes described as being "immobilized by anxiety,"[197,198] and reduced GABAergic binding has been identified in the right orbitofrontal cortex of patients in catatonic states.[199] Northoff et al assessed the subjective experience of 22 patients with catatonia, after they had recovered from the acute state. They rated their experience of anxiety and feeling overwhelmed as comparable to patients with major depression. Catatonic patients who had an immediate response to lorazepam, a benzodiazepine, described more subjective distress than those who did not have an immediate response to lorazepam. Lastly, the fact that catatonia is often more characteristic of bipolar disorder than schizophrenia[200] is very much in line with our formulation of stress vulnerability as a transdiagnostic facet of psychiatric phenomenology.

Studies of New GABAergic Agents

What are the implications of our model for new treatments? Benzodiazepines have limited efficacy and many downsides, such as poor selectivity for GABAR subtypes and high liability for abuse. The fact that they are not more effective in the treatment of schizophrenia likely reflects the complexity of GABA and its regulation, with multiple points of modulation. Subtype selective agents for GABAR have been examined. A study with an

α–2/3 selective subtype for the GABAR initially showed promise, including the ability to enhance gamma activity linked to PVBC,[201] only to fail in a larger, controlled trial.[202] However, relative to chlorodiazepoxide, this compound only had 11% efficacy at α-2 GABAR.[186] Other possibilities include α-5 selective drugs, which have shown promise in reducing DA hyperactivity in a rodent model.[203] Another target is the Kv3.1 family of potassium channel,[204] highly localized to PV+ neurons, and found to be deficient in neocortex of schizophrenia patients in postmortem work.[205] Most importantly, if, as we argue, NA is a relevant clinical phenotype of GABAergic dysfunction, then pharmacologic strategies targeting GABA and PVI would do well to screen for effects on NA, in addition to the usual assays typically used for schizophrenia drugs. There is a growing recognition in the field that managing susceptibility to stress and reducing NA is a critical part of treating schizophrenia patients, particularly in the early phase of the illness and for people at high risk of psychosis.[206,207]

Conclusion

We have presented a model of stress vulnerability in schizophrenia, connecting this trait vulnerability with an overall tendency to experience NA. NA represents an independent symptom dimension of schizophrenia, although it interacts with other symptoms, and it is strongly associated with poor functional outcome. Our model proposes that GABAergic dysfunction, specifically of PVI, may be one of the root causes of the vulnerability. This hypothesis builds upon postmortem findings and animal models, but we recognize that a large gulf exists between these evidence domains and the clinical phenotype, and no data has yet made a direct link between PVI abnormalities observed in postmortem data and any clinical condition. As we mention at the outset, the postmortem findings cut across diagnoses, and we predict the relationship between PVI, vulnerability and NA is a transdiagnostic one. For example, there is a significant literature implicating GABAergic mechanisms in depression,[208–210] and transdiagnostic studies will be required to determine how much overlap these mechanisms have with NA in schizophrenia. With emerging technologies and focused hypotheses, linkages between the molecular-cellular, circuit-level, and clinical phenotype should be able to parse PVI vulnerability from other forms of NA in schizophrenia, and other major psychiatric disorders.

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