We were very pleased to read the excellent article by Taylor and colleagues, which has highlighted the central role of the GABAergic system in determining stress vulnerability and modulation of negative affect (NA) in schizophrenia.

We fully agree that the relevance of GABAergic system goes far beyond schizophrenia, because GABAergic dysfunction might be responsible for a number of affective, behavioral, and cognitive symptoms through neurodevelopmental disturbance of emotional regulation across several mental disorders. Here, we propose that a first step toward better understanding of the transdiagnostic contributions of aberrant GABAergic system would be through investigating catatonia in the literal sense of the terms “psycho” and “motor.” Catatonia is one of the oldest syndromes described in clinical psychiatry which occurs in 9%–17% of acute mental disorders and is characterized by a triad of affective, motor, and behavioral symptoms. Catatonia can be classified as “catatonic schizophrenia” in ICD-10 and as “catatonia not otherwise specified,” that is, as residual category in DSM-5. In DSM-5, unlike in ICD-10, catatonia is also linked to other mental disorders or specific medical conditions. Still, there is intensive effort to recognize catatonia as an independent diagnostic entity in ICD-11.

For about a decade, the RDoC initiative provides a platform for neuroscientific research of mental disorders based on dimensions of observable behavior and neurobiological measures. In line with this framework, there are two main reasons to support catatonia as a paradigmatic model for RDoC-based investigation of GABAergic system:

(1) Clinical syndrome and its pathophysiological basis: The precise clinical description of former psychiatrists could achieve a good differentiation of catatonia as a psychomotor syndrome from other psychiatric disorders including both affective and schizophrenic psychoses. More recent researchers showed that catatonia characterized by its three symptom dimensions (motor, affective, and behavioral) is based on dysfunction of GABAergic cortical circuits. Targeting the GABAergic system in frontoparietal regions with lorazepam (positive allosteric modulation at the GABAA receptor) or GABAergic mediated electroconvulsive therapy (ECT) leads to an improvement of motor, affective and behavioral symptoms not only in schizophrenia, but also in autism and affective disorders. This is in line with Taylor and colleagues and their emphasis on the relation of GABA and NA as catatonic patients often experience/show extreme uncontrollable fear and anxiety from which they can be relieved by GABAergic drugs. Hence, the case of catatonia strongly extend the dimensional as well as the syndromal nature of GABA and NA beyond schizophrenia as emphasized by Taylor and colleagues.

(2) Future directions: We expect that the different levels of the relation of GABA and NA can be extended even more in the future in the case of catatonia. There is a mechanistic animal model of catatonia, which will help us to understand genes, molecules, and cells of the GABAergic system in mice and men. Catatonic symptoms can be easily measured using instrumental assessments for detecting sensorimotor dysfunction and multimodal MRI. That’s what makes the investigation of aberrant circuits, physiology, and behavior associated with GABAergic dysfunction so convenient. Studying the dysfunction of the GABAergic system (dysbalance between GABA$_A$ and GABA$_B$) in animal models and human beings will help to reduce the risk of failure in clinical trials (which we are still lacking). Multimodal MRI research on catatonia will provide important clues to the complex interplay between dysfunctions and dynamics of neural circuitry underlying sensorimotor function, behavior,
affective processing, and cognition. In particular, we will better delineate the interaction between basal ganglia, cerebellar, and cortico-motor circuits, which are not solely responsible for sensorimotor function/dysfunction. Not to be forgotten are also first-person reports or citations of patients’ statements to investigate the structure of patients’ subjective (a priori) experience (eg, following a phenomenological approach) before and after development of catatonic symptoms. Therefore, we strongly endorse the notion that mental disorders must be understood as a dysfunction of individual neurotransmitter systems with a focus on specifically GABA and associated brain circuits (and not as rigid categories) to develop neurobiologically plausible therapies.

Finally, catatonia can be defined as primarily “psycho” and “motor” disorder that is based on dysbalance between GABAergic and serotonergic as well as dopaminergic neurotransmission that essentially modulates both affective and motor systems, as well as their cortico-subcortical functional interplay. Pathophysiology- and dimension-based research framework on catatonia as proposed by RDoC initiative does not only open the door for developing more proper treatment of this devastating condition but also into the psycho-motor, for example, affective-motor and cognitive-motor mechanisms and functions of the healthy brain.

Acknowledgment
The authors have declared that there are no conflicts of interest in relation to the subject of this commentary.

References