plied in psychiatric genomics in the coming years, it has limitations imposed by the fact that it works by stitching together short reads *in silico*. This means that there are regions of the genome which are difficult or impossible to read, such as those containing large structural variants, repetitive sequences, extreme guanine-cytosine content, or sequences with multiple homologous elements within the genome. This is sometimes known as the "dark genome".

There are now a number of long-read sequencing (LRS) platforms that allow the analysis of segments of the human genome up to 200kb, and these are capable of shining a light into the dark genome. Emerging studies using LRS are identifying larger, more harmful structural variants and long repetitive elements[7,9], both of which are candidates for involvement in psychiatric disorders.

Psychiatric genomics is a work in progress. GWAS have been hugely successful in identifying the role of multiple common variants, but recent work on missing heritability suggests a need to focus now on rare variants, and in the next few years we can expect studies based upon both SRS and LRS technologies to do this.

Fully characterizing the genetic architecture of psychiatric disorders is likely to improve polygenic risk prediction for both screening and stratification, allow a better understanding of the underlying biological mechanisms of disease, and broaden the landscape of pharmaceutical targets[2].

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Toward a systems-based approach to understanding the role of the sympathetic nervous system in depression

The sympathetic nervous system (SNS) has an essential role in the prototypical stress response. Stress, stressors, and stress responses are central themes in most prominent theories of depression etiology and maintenance. Yet, the SNS is not a commonly targeted mechanism in depression research. Here we propose a dynamic, systems-level approach that contextualizes SNS-mediated stress responsivity within a regulatory framework. We believe that this conceptualization hews closer to the role of the SNS as a time-varying, context-driven regulatory system, and provides clinicians and researchers with a model for understanding its relevance to depression.

Interest in the SNS in depression is not new. A host of methods and markers have been used to try to delineate the role of the SNS in depression, including cardiac measures such as heart rate and pre-ejection period, skin conductance, salivary alpha-amylase, and urinary and serum measures of catecholamines. However, evidence for tonically-elevated SNS arousal in depression has been inconsistent and equivocal[1].

We propose three reasons for this equivocality. First, because the SNS is embedded in a larger set of regulatory systems, analysis of absolute levels should be augmented with – if not eschewed altogether for – a systems perspective that incorporates dynamic interrelations between system components. Second, the temporal dynamics of the stress response have been well documented[2], with SNS effects occurring relatively rapidly and ephemerally (compared to those of glucocorticoids), and attempts should be made to capture these time-dependent fluctuations. Third, there are likely to be individual differences in the dynamics and calibration of cognitive, affective and physiological regulatory systems. Thus, attempts should be made to identify subgroups.

Cognitive theories of depression have long posited the importance of depressogenic schemas – internal working models of the self, others, and the world – that magnify and distort the perception of ambiguous stimuli[3]. The presence of these schemas can increase the likelihood of threat appraisals (e.g., perceptions of external stressors) and the elicitation of negative emotional responses. The aversive arousal from negative emotions has been proposed to amplify memory for negative events[2] and provide experiential feedback that supports and reinforces the initial threat appraisal[3]. Thus, individuals with depression may be more likely to perceive environmental stressors, which elicit negative emotional reactions that reinforce the threatening nature of the stimulus and enhance memory encoding of the experience.

Inherent to this positive feedback loop between perceptions, appraisals and arousal is the physiological stress response to perceived stressors. This response serves an adaptive function to mobilize energy, stimulate immune activation, and increase cardiovascular tone through vasoconstriction and increases in heart rate and contractility. The stress response is composed of coordinated actions of the hypothalamic-pituitary-adrenal (HPA) axis, the SNS and the parasympathetic nervous system (PNS).

Compared to the SNS, there has been an abundant amount of research on the HPA axis and the PNS in depression, and studies have found evidence for HPA dysfunction[4] and reduced heart rate variability[1,5] in depressed patients. However, contradictory and null findings have also been common. We raise the possibility that inconsistent findings may stem from the isolation of system components in lieu of the whole. For instance, the HPA axis

can play permissive or suppressive roles in determining the magnitude of SNS stress reactivity[2]. Because HPA axis functionality can precede and inform the nature of the sympathetic stress response, incorporating preceding levels of available cortisol *in situ* during moments of emotional strain may help to better calibrate measurements of SNS reactivity in dysphoric individuals.

Moreover, it has been demonstrated that the doctrine of reciprocal antagonism between the PNS and SNS – the notion that more of one inherently means less of the other – does not universally hold[6]. This conclusion dictates that the two systems can exhibit concurrent and interactive behavior and should be measured and modeled as separate and distinct dimensions. A systems approach to stress responsiveness may help to better define and measure the individual components.

However, methodological challenges remain regarding the measurement and timing of different system components. The cascade of HPA axis hormonal actions has been well documented, with peak effects following roughly 20 min after stress exposure[2]. Meanwhile, PNS effects such as vagal withdrawal can operate on a scale of milliseconds to seconds, and SNS effects typically take place on a scale of seconds to minutes. We propose that research into autonomic functioning in human subjects should be pursued via time series analysis of electrophysiological measurements.

Common inputs such as respiratory sinus arrhythmia, pre-ejection period, and heart rate can be binned in epochs as small as 30 sec. Thus, data collection periods as short as an hour can produce time series of 120 observations. Time series analyses such as vector-autoregression and network analysis can model the relationships between system components. Moreover, ambulatory technologies exist allowing researchers to capture autonomic functioning in emotionally salient scenarios during an individual's day-to-day life.

Measures such as pre-ejection period require academic-research-grade equipment and expertly placed electrodes. However, innovations in mobile assaying of salivary measures could yield ambulatory measurements of SNS markers such as salivary alpha-amylase. Additionally, one could foresee the development of a fingerstick system for capillary blood measurement of catecholamines akin to blood glucose monitoring systems. It has been shown that reliable measurements of catecholamines can be derived from as little as 100 μL of capillary blood[7].

Understanding the role of the SNS in the treatment of depression may be important for patients' psychological and physical health. As noted above, depressed individuals have been shown to have significantly decreased parasympathetic cardiac regulation, and depression has long been associated with an increased incidence of coronary heart disease[1,5]. Although the evidence for sympathetic predominance in depressed patients has been equivocal, there is some evidence that antidepressant medications may affect this predominance[8]. Of note, one study has found that cognitive behavioral treatment may increase heart rate variability[9]. Clearly, more work is needed to understand the effects of psychotherapy and antidepressant medications on the SNS and sympathetic cardiac control.

Finally, we noted at the outset the likely existence of heterogeneous subpopulations of depressed individuals, some of whom may experience elevations in sympathetic arousal and some may not. It follows that individuals could exhibit more complex individual differences in the calibration of stress responsivity among cognitive, affective and physiological system components.

From this perspective, the SNS could play a primary role in driving phenomenological and physiological consequences for some individuals. For instance, during the transduction of cognitive-emotional stimuli into physiological responses, an adrenergic gain factor might serve to amplify moderate signals into more robust responses. In a time series context, competing directional models of SNS arousal, subjective affect, and cognitive appraisal could be tested. Moreover, such evaluations could be carried out on a person-by-person basis.

The SNS plays a calibrating role, exerting effects in response to shifting external demands and emotional conditions. It may be more fruitful to examine these dynamic, time-varying relationships with other stress-response systems, rather than mean group differences.

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Cardiac vagal tone: a neurophysiological mechanism that evolved in mammals to dampen threat reactions and promote sociality

The evolutionary journey from asocial reptiles to social mammals is highlighted by a reorganized autonomic nervous system with unique structural and functional changes in the vagus. These changes enable mammals to suppress defensive strategies in order to support and express sociality. The product of this transition is an autonomic nervous system with capacities to self-calm, to socially engage others, and to mitigate threat reactions in ourselves and others through social cues.