Interoception abnormalities in schizophrenia: A review of preliminary evidence and an integration with Bayesian accounts of psychosis

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ABSTRACT

Schizophrenia research has traditionally focused almost exclusively on how the brain interprets the outside world. However, our internal bodily milieu is also central to how we interpret the world and construct our reality: signals from within the body are critical for not only basic survival, but also a wide range of brain functions from basic perception, emotion, and motivation, to sense of self. In this article, we propose that interoception—the processing of bodily signals—may have implications for a wide range of clinical symptoms in schizophrenia and may thus provide key insights into illness mechanisms. We start with an overview of interoception pathways. Then we provide a review of direct and indirect findings in various interoceptive systems in schizophrenia and interpret these findings in the context of computational frameworks that model interoception as hierarchical Bayesian inference. Finally, we propose a conceptual model of how altered interoceptive inference may contribute to specific schizophrenia symptoms—negative symptoms in particular—and suggest directions for future research, including potential new avenues of treatment.

1. Introduction

Schizophrenia is a severe mental illness that affects 1 in every 100 individuals in the world. Persons with schizophrenia experience positive symptoms (hallucinations and delusions), negative symptoms (decreases in motivation and emotional expression), and disorganized symptoms (disruptions in thought processes), as well as basic cognitive impairments (Keefe and Harvey, 2012). Schizophrenia is associated with substantially shortened life expectancy, approximately 20 years below that of the general population (Laursen et al., 2014). Even with pharmacological and psychosocial treatments, only 1 in every 7 individuals reach standard recovery metrics (Jaaskelainen et al., 2013). Current treatments for schizophrenia fall short because symptom mechanisms are largely unknown. However, recent shifts away from studying circumscribed neural circuits and neuromodulatory systems in schizophrenia, and instead towards computational, multi-level, network-based approaches to understanding the wide range of cognitive impairments and clinical symptomatology, hold the promise to yield clinically-relevant insights into symptom mechanisms (Adams, 2018).

Such frameworks have provided valuable insights into how the brain interprets the external world and how alterations in that process may lead to departures from consensual reality (Corlett et al., 2016; Fletcher and Frith, 2009). However, our internal bodily milieu is also central to how we interpret the world and construct our reality (Tsakiris and De Preester, 2019). Indeed, a situation that is accompanied by our hearts beating wildly will be interpreted differently from the same situation that is met by an imperceptible change in our bodily rhythms. The processing of bodily signals has been largely left out of broad explanatory accounts of schizophrenia symptoms. In this article, we would like to argue that interoception may provide key insights into understanding illness mechanisms of schizophrenia.

Interoceptive processing refers to the sensing, integration, and interpretation of bodily signals from anywhere within the body (Khalsa et al., 2018). It is more than visceral senses as autonomic, hormonal, and immunological signals may also contribute to our overall perception of the physiological state of our body (Barrett and Simons, 2015). This crosstalk between brain and body promotes survival through autonomic functions (e.g., adjusting blood pressure or body temperature) as well as adaptive behaviors (e.g., seeking food or water). The conventional view of homeostasis posits that the brain tries to keep all internal systems within certain “set points” (e.g., a narrow range of normal body temperature) for healthy functioning, and only initiates regulatory actions...
when a system deviates from its set point. However, this is likely not the complete picture of how our brain regulates our body. The updated allostatic model posits that homeostasis alone is inefficient and can hardly meet an animal’s changing energy needs in a natural environment. Rather, the more energy-efficient mechanism is to constantly predict the metabolic needs that may arise in the next moment and adjust and prepare the body accordingly (e.g., drink before we feel thirsty, put on gloves before we get frostbite). Under this predictive framework, interoception is integral to how the brain regulates an animal’s internal milieu to promote survival and reproduction (Schulkin and Sterling, 2019; Sterling, 2012). In this way, interoception and allostatic can be understood as a perception-action loop - interoception enables allostatic, and allostatic results in bodily changes that create interoceptive feedback (Fig. 1). In this article, we use “interoception-allostatic” when referring to the complete loop from sensing, integrating, and interpreting bodily signals to acting upon them, and “interoception” alone when referring to sensing, integrating, and interpreting.

Interoception is not only proximal to our survival, however, but also influences a wide range of brain functions that are commonly altered in schizophrenia, such as basic exteroceptive sensory perception (sensing signals from outside the body), processing speed, reasoning, emotion, motivation, and our sense of self (Makowski et al., 2020; Pramme et al., 2016, 2014; Tsakiris and De Preester, 2019). For example, our hearts generate rhythmic electrical signals (Azzalini et al., 2019) and several brain regions reset their firing phase shortly following each heart contraction (Park et al., 2018), presumably to facilitate the processing of external signals according to how relevant they are to the body (Babo-Rebelo and Tallon-Baudry, 2019). Indeed, such neurocardiac coordination immediately prior to the onset of a faint visual stimulus predicts whether the stimulus is consciously perceived (Park et al., 2014), demonstrating the delicate interaction between the processing of input from the external world and from one’s own body.

Given the widespread involvement of interoception in cognition, emotion, and perception of the outside world and existing evidence of interoceptive abnormalities in schizophrenia (see later sections), one may surmise that disrupted interoception may play a role in both positive and negative symptoms of schizophrenia. For example, one may develop the delusional sense of something ominous impending when there is no clear explanation for intense bodily sensations (Pezzulo, 2014). On the other hand, a blunted experience of one’s bodily sensations may lead to the disturbances in body ownership or agency (Allen and Tsakiris, 2019; Seth, 2013; Tsakiris, 2017). Over time, the constant sense of uncertainty around the cause of bodily sensations may lead to a generalized sense of low self-efficacy (Stephan et al., 2016). This may further develop into negative symptoms such as reduced level of activity and social isolation, as an attempt to reduce uncertainty. Therefore, exploring how persons with schizophrenia experience their bodies and interpret their bodily signals is potentially key to understanding illness mechanisms.

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In light of recent developments in the mechanistic understanding of interoception (Tsakiris and De Preester, 2019), this article aims to critically examine the existing literature on interoception in persons with schizophrenia and to propose an explanation of these findings in the context of existing computational frameworks for understanding symptoms of schizophrenia. Specifically, we start with a brief overview of interoception and interoceptive pathways, followed by a review of existing findings in various interoceptive systems in schizophrenia. Next, we introduce the notion of interoception as hierarchical Bayesian inference and interpret interoception findings in schizophrenia through this interoceptive inference framework. Finally, we propose a conceptual model of how altered interoceptive inference may contribute to specific schizophrenia symptoms and suggest directions for future research.

**Fig. 1.** A schematic illustration of the interoception-allostatic process. In general, interoceptive signals are generated by corresponding organs or stimuli, registered by various receptors, transmitted through the spinal cord and cranial nerves, integrated and interpreted by the central nervous system, and regulated by the autonomic nervous system. Theoretically, abnormal interoception could reflect alterations at any of these steps.
2. Interoception in schizophrenia: a review

2.1. Interoception pathways

A key part of the interoception-allostasis process (Fig. 1) is supported by the autonomic nervous system, which regulates bodily functioning and acts largely outside conscious awareness (Bernston et al., 2019). Therefore, interoception-allostasis is typically below our conscious perceptive thresholds. Furthermore, the conscious perception of bodily states typically emerges through the integration of signals from multiple interoceptive systems across different temporal scales. For example, the simple feeling of breathlessness can involve signals from up to 16 different sources, including mechanoreceptors in the lungs, chemoreceptors in muscles and the brain stem, vascular and skin receptors, corollary discharge signals from the respiratory motor system, and many others (Parshall et al., 2012). Consequently, when interoception rises to the level of conscious awareness, it is often vague, diffuse, and not well-localized.

Interoceptive afferent signals originate from sources all over the body, including chemoreceptors, humoral receptors, mechanoreceptors, and nociceptors (Bernston and Khalsa, 2021). These signals are mainly relayed through the spinal cord and cranial nerves, especially the vagus nerve (Yuan and Silberstein, 2016). Initial processing and integration of the afferent signals transpires within autonomic ganglia and the spinal cord (Craig, 2002; Critchley and Harrison, 2013; Jänig, 1996), before the inputs project to cell groups in the brainstem. Interceptive afferents are further processed in subcortical (thalamus, hypothalamus, hippocampus, and amygdala) and cortical regions (insula and somatosensory cortices; Khalsa et al., 2018). The insula, in coordination with anterior cingulate and ventromedial/orbitofrontal cortex, plays a critical role in integrating interoceptive signals in order to form higher order representations of bodily states (Quadt et al., 2018) that can be further integrated with exteroceptive signals (Nguyen et al., 2016).

2.2. Direct experimental evidence for altered interoception in schizophrenia

To date, only four studies have directly examined interoception in schizophrenia (Ardizzi et al., 2016; Critchley et al., 2019; Koreki et al., 2020; Torregrossa et al., 2021). All four studies found that persons with schizophrenia exhibited lower interoceptive accuracy, as measured by objective performance on an interoception task. Specifically, they performed less accurately than healthy participants on a heartbeat counting task (Schandry, 1981) that required the participant to estimate how many times their heart beat over different time intervals. On the other hand, relationships between interoceptive accuracy and clinical symptoms are mixed. In one study, better interoceptive accuracy was associated with more severe positive symptoms (Ardizzi et al., 2016), while another found that poorer interoceptive accuracy was associated with more severe positive and negative symptoms (Koreki et al., 2020), and a third found no relationship between symptoms and interoceptive measures (Torregrossa et al., 2021). Two studies investigated interoceptive sensibility in individuals with schizophrenia. Interoceptive sensibility refers to one’s subjective belief about their sensitivity to bodily states and is typically operationalized as either confidence in interoceptive task performance without knowledge of one’s accuracy, or as self-reported ability to notice subtle changes in one’s bodily states. Interoceptive sensibility was also noted to be altered in persons with schizophrenia (Koreki et al., 2020; Torregrossa et al., 2021), but the nature of such difference was inconsistent. Only one study examined interoceptive awareness in persons with schizophrenia. Interoceptive awareness refers to one’s metacognitive insight into their interoceptive aptitude. It is typically operationalized as the trial-to-trial correspondence between performance accuracy and confidence on an interoceptive task. In this study, interoceptive awareness was found to be intact in persons with schizophrenia, but potentially moderated by antipsychotic medications (Torregrossa et al., 2021). Note that previous studies suggest that interoceptive accuracy, sensibility, and awareness are dissociable and only correlate with each other in individuals with high interoceptive accuracy (Garfinkel et al., 2015). Complicating the interpretation of these findings, however, is recent evidence suggesting that the performance on the heartbeat counting task may have little to do with interoception because participants can base their estimation of heartbeat frequency solely on prior knowledge and beliefs of heart rate (see Brener and Ring, 2016; Ring and Breran, 2018). Thus, conclusions about interoceptive accuracy based on the heartbeat counting task are limited, and potentially undermined, by poor task validity.

2.3. Indirect evidence from interoceptive systems

Though there is very little direct evidence on interoceptive accuracy, sensibility, or awareness in schizophrenia, there is a body of literature describing dysfunction in various bodily systems in this population that dates as far back as a century ago, and such dysfunction may contribute to or reflect interoceptive abnormalities in individuals with schizophrenia. This section, which is organized by specific organs and bodily systems, provides a review of this literature (see Table 1 for a summary of key findings). Because the primary aim of these studies was not to investigate interoception, it is oftentimes impossible to deduce from the findings whether altered bodily functioning was due to altered functioning of the organ, the registration and transmission of the interoceptive signals (through peripheral and/or central mechanisms), the interpretation of the interoceptive signals (within the central nervous system), or the autonomic regulation in response to interoceptive signals (see Fig. 1). In other words, findings reviewed in this section may point to alterations in the body, the brain, and/or the communication between the body and the brain; however, given that these alterations span multiple bodily systems, we may suspect that they are rooted in shared brain or brain-body mechanisms. Though we cannot pinpoint the exact cause of bodily dysfunctions reviewed here, these findings nonetheless may be broadly relevant to interoception-allostasis and to clinical symptoms and subjective experience in schizophrenia. We will discuss potential interpretations of these findings and their implications for understanding interoception in schizophrenia in later sections. We acknowledge that some of the physiological alterations reviewed here may appear at first glance somewhat tangential to interoception; however, interoceptive dysfunction stands to engender long-term changes in homeostatic equilibrium—a topic to which we later return.

Furthermore, the effect of medications and medical comorbidities muddy a clear interpretation of this literature. For the purpose of this review, we will not discuss instances where altered interoception is directly secondary to a known medical condition (e.g., diabetic neuropathy), unless the finding persists after controlling for all known medical causes. Similarly, medications can lead to changes in bodily functions and interoception, and may thus confound group differences. Therefore, we will discuss potential medication effects when there is relevant literature.

2.3.1. Cardiovascular system

Our brain constantly adjusts our heart rate in response to environmental changes and metabolic demands through the baroreflex, with heart rate acceleration and deceleration mediated by sympathetic and parasympathetic activity, respectively (Thayer et al., 2009). The sensation of heartbeats is mainly relayed from baroreceptors in the aorta and carotids to the brainstem via the vagus nerve. The natural beat-to-beat fluctuation in heart rate, termed heart rate variability (HRV), is interpreted as a marker of autonomic regulation. More specifically, the high frequency (0.15–0.4 Hz) component of HRV (HF-HRV) is deemed a sensitive measure of vagal modulation of heart rate, likely regulated by prefrontal inhibitory control over the autonomic nervous system (Thayer et al., 2009). Therefore, low HRV (i.e., a
Summary of key findings of altered interoceptive system functioning in persons with schizophrenia.

<table>
<thead>
<tr>
<th>System</th>
<th>Findings in Schizophrenia (and Unaffected Relatives)</th>
<th>Study/Review/Meta-analysis</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>increased heart rate</td>
<td>Akar et al. (2015), Ardizzi et al. (2016) and Mathewson et al. (2012)</td>
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<td></td>
<td>reduced Heart Rate Variability (HRV)</td>
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<td></td>
<td>most antipsychotics do not affect HRV, but Clozapine significantly reduces it</td>
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<td></td>
<td>reduced HRV in healthy first-degree relatives</td>
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<td></td>
<td>reduced HRV correlated with more severe positive symptoms</td>
<td>Cella et al. (2018) and Kimby et al. (2017)</td>
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<td></td>
<td>lower resting respiratory sinus arrhythmia (RSA) correlated with more severe negative symptoms and worse executive functioning</td>
<td>Mathewson et al. (2012)</td>
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<td></td>
<td>lower maximal oxygen uptake during cardiopulmonary exercise</td>
<td>Vancampfort et al. (2015)</td>
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<td></td>
<td>impaired lung function at rest, suggesting restricted lung volumes</td>
<td>Partti et al. (2015)</td>
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<td></td>
<td>increased rates of respiratory disease</td>
<td>Suetani et al. (2021)</td>
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<tr>
<td>Respiratory</td>
<td>unmedicated patients have increased breathing rate</td>
<td>Peupelmann et al. (2009a)</td>
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<td></td>
<td>unmedicated patients have decreased synchrony between heart rate and respiration</td>
<td>Vancampfort et al. (2015)</td>
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<td></td>
<td>low maximal oxygen uptake correlated with more severe negative symptoms</td>
<td>Hsu et al. (2017)</td>
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<td></td>
<td>higher risk of urinary incontinence</td>
<td>Hyde et al. (2008)</td>
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<td></td>
<td>higher rate of childhood enuresis</td>
<td>Hall et al. (2012)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>increased prevalence of lower urinary tract symptoms with atypical antipsychotics use in women, but not in men</td>
<td>Manu et al. (2015) and Hansen et al. (2011)</td>
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<tr>
<td></td>
<td>increased tachygastria in unmedicated patients, correlated with more severe delusions</td>
<td>Peupelmann et al. (2009b)</td>
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<td></td>
<td>substantial weight gain due to antipsychotic use and other factors</td>
<td>Spelman et al. (2007)</td>
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<tr>
<td>Gastrointestinal</td>
<td>impaired glucose regulation in healthy first-degree relatives</td>
<td>Waltz et al. (2015)</td>
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<td></td>
<td>reduced sensitivity to change in satiety</td>
<td>Sailer et al. (2017)</td>
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<td></td>
<td>Higher rate of primary polydipsia and hyponatremia</td>
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<td>reduced pain sensitivity in controlled experiment settings, regardless of antipsychotic exposure, moderated by psychiatric symptom severity</td>
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<td></td>
<td>higher sensory threshold and lower physiological response to noxious stimuli</td>
<td>de la Fuente-Sandoval et al. (2010)</td>
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<td>Nociceptive</td>
<td>healthy relatives</td>
<td>Hooley and Delgado (2001)</td>
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<td></td>
<td>significant reduction in pain sensitivity after antipsychotics onset</td>
<td>Stubb et al. (2015)</td>
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<td></td>
<td>same prevalence of reported pain in clinical settings (despite more physical comorbidities)</td>
<td>Stubb et al. (2014)</td>
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<td></td>
<td>over-activation of the primary somatosensory cortex, but</td>
<td>de la Fuente-Sandoval et al. (2010)</td>
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lack of beat-to-beat heart rate adjustment), especially low HF-HRV, is interpreted as a lack of inhibitory influence from the prefrontal cortex (Thayer et al., 2009). Similarly, there is growing evidence that higher HRV is associated with a wide range of positive outcomes including better emotion regulation (Appelhans and Luecken, 2006), greater sustained attention, working memory, and motor-response control (Thayer et al., 2009), better glucose regulation, and reduced inflammation (Thayer and Sternberg, 2006).

Findings of increased heart rate (Akar et al., 2015; Ardizzi et al., 2016; Mathewson et al., 2012) and reduced HRV (see Clamor et al., 2016 for a meta-analysis) in individuals with schizophrenia compared to healthy controls have been widely replicated. However, the relationship between HRV and clinical symptoms has not been well-studied, and findings are mixed. Two studies found that reduced HRV was correlated with more severe positive symptoms both across (Cella et al., 2018) and within persons with schizophrenia (Kimhy et al., 2017), suggesting a relationship between autonomic arousal (or failure to maintain sufficient parasympathetic regulation) and worsening of positive symptoms. Another study found that lower respiratory sinus arrhythmia (RSA, an index of respiration-driven heart rate changes mediated by vagal control) in persons with schizophrenia was correlated with more severe negative symptoms and worse performance on an executive functioning task (Mathewson et al., 2012), supporting the putative role of prefrontal cortex in inhibitory control of both physiological and cognitive processes.

Contrary to earlier belief, a recent meta-analysis revealed that the impact of antipsychotic medication on HRV in schizophrenia is small and largely non-significant, with clozapine being the only exception that significantly reduces HRV (Alvares et al., 2016). Moreover, unaffacted and unmedicated first-degree relatives of persons with schizophrenia exhibited similarly reduced HRV (Bár et al., 2009), further supporting that low vagal tone was not due to chronic antipsychotic exposure. In fact, one recent meta-analysis suggested that reduced vagal tone (as indexed by lower HF-HRV) should be considered a potential endophenotype for schizophrenia (Clamor et al., 2016).

2.3.2. Respiratory system

Respiratory sensations (e.g., tightness in the chest, urge to cough, air-hunger, sense of lung volume and airflow, etc.) are predominantly relayed from various sensory neurons in the bronchi and the lungs to the brainstem by the vagus nerve (Widdicombe, 2009). Corollary discharge signals (i.e., copies of motor commands sent to sensory brain regions) from brainstem and respiratory motor areas of the brain likely also contribute to different respiratory sensations (Parshati et al., 2012).

There is consistent evidence that persons with schizophrenia have impaired lung function after controlling for co-morbid medical conditions and level of activity (see Suetani et al., 2021; Vancampfort et al.,...
2015 for review and meta-analysis). Even after reviewing for age, gender, smoking status, abdominal obesity, type 2 diabetes, metabolic syndrome, and amount of physical activity, schizophrenia remained a significant predictor of suboptimal lung function (Partti et al., 2015). Moreover, neuroleptics may have only limited influence on respiratory abnormalities in schizophrenia. For example, unmedicated persons with schizophrenia have increased baseline breathing rate and decreased synchrony between heart rate and respiratory rate, suggesting a lack of regulatory control from the brainstem (Petropoulos et al., 2009a).

There is accumulating evidence suggesting an association between altered breathing pattern and negative symptoms in persons with schizophrenia, but more research is needed to rule out confounding factors such as body mass index (BMI), medications, and physical comorbidities. Low cardiorespiratory fitness in persons with chronic schizophrenia was consistently found to be correlated with more severe negative symptoms (see Vancampfort et al., 2015 for review and meta-analysis), even when controlling for lifestyle and medical conditions (Kimhy et al., 2014; Vancampfort et al., 2014). On the other hand, associations between poor cardiorespiratory fitness and more severe positive symptoms (Strassig et al., 2011) and lower global functioning (Rosenbaum et al., 2015) have also been reported.

2.3.3. Genitourinary system

The decision to void is more than just a reflex to visceral sensations, but a strictly controlled process determined by one’s emotional state and the social appropriateness of the situation as assessed by higher centers such as the insula, thalamus, anterior cingulate gyrus, and prefrontal cortex (Fowler et al., 2008).

In the early 1900s, Kraepelin described more frequent urinary incontinence in persons with schizophrenia (Kraepelin, 1971). These early clinical observations are supported by recent findings that the risk of urinary incontinence is nearly twice as high in persons with schizophrenia than in the general population, even after controlling for medications and medical comorbidities (Hsu et al., 2017). Another study in an inpatient setting found that persons with schizophrenia had a higher incidence of urge incontinence (loss of urine due to a sudden strong urge to urinate) and bed wetting than persons with a mood disorder (Bonney et al., 1997), despite no difference in stress incontinence (loss of urine due to pressure on bladder caused by physical movements such as coughing and heavy lifting). Importantly, the two groups did not differ in urinary urgency, suggesting that the higher incidence of urge incontinence in individuals with schizophrenia may arise from a reduced influence of signals from higher centers in the brain that determine the temporal and social appropriateness of urination (Fowler et al., 2008).

Current evidence suggests that atypical antipsychotic medications are associated with adverse urinary symptoms in women, but not in men (Hall et al., 2012, but see Holtmann et al., 2003). Arguing against the idea that urinary incontinence is exclusively secondary to medication are findings that persons with schizophrenia have a higher rate of childhood enuresis than their unaffected siblings and healthy controls (Hyde et al., 2008). Those patients with a history of enuresis also showed poorer cognitive performance and reduced grey matter volume in frontal and parietal cortex, when compared with patients with no history of enuresis. These results suggest that poor bladder control may manifest in the premorbid period of schizophrenia and may be associated with delayed prefrontal maturation (Hyde et al., 2008) or impaired prefrontal regulation. There are also case reports of persons with schizophrenia who had resolved childhood enuresis but later developed recurrent urinary incontinence, further supporting a neurogenic cause for their bladder dysfunction (Gupta et al., 1995).

2.3.4. Gastrointestinal system

Information about the conditions of the gut (e.g., pressure, stretch, distortion), nutrient-related signals, and immune signals are transmitted to the central nervous system mainly through vagal and spinal afferent neurons (Mayer, 2011). These gut related interoceptive signals (e.g., abdominal pain and discomfort, nausea, hunger) are primarily processed and integrated in the anterior insula and orbitofrontal cortex, and further modulated by input from other brain regions, such as prefrontal cortex, hypothalamus, and anterior cingulate cortex.

There is preliminary evidence that persons with schizophrenia experience satiety differently and may have abnormal gastric electrical activities. One study found that individuals with schizophrenia report lower levels of satiety than healthy controls following a similar amount of food consumption (Waltz et al., 2015); however, it is unclear whether this effect was due to higher rates of obesity in persons with schizophrenia, as obesity is associated with delayed satiation and accelerated gastric emptying of solids and liquids (Acosta et al., 2015). In addition, unmedicated persons with schizophrenia exhibited increased tachygastria, an increased rate of electrical pacemaker activity in the stomach that is indicative of sympathetic activity (Peupelmann et al., 2009b). Moreover, such increased sympathetic modulation in the enteric nervous system was more prominent in those with more severe delusions.

Schizophrenia is furthermore associated with significant weight gain that is partly (Mans et al., 2015), but not entirely, due to antipsychotic use. To maintain a healthy weight and optimal energy regulation, blood glucose level is maintained within a narrow range by hormones like insulin and glucagon (Aronoff et al., 2004). Glucose regulation is impaired even in first-episode, drug-naive individuals with schizophrenia with normal BMI and no comorbid medical conditions (Spelman et al., 2007). Moreover, impaired glucose regulation is similarly elevated in unaffected first-degree relatives of individuals with schizophrenia, suggesting a shared genetic or environmental factor that is not related to antipsychotic exposure. Interestingly, in a population-based genome-wide association study, a well-known diabetes risk gene variant is found to be associated with schizophrenia (Hansen et al., 2011), potentially indicating common mechanisms underlying the psychiatric and metabolic conditions, such as inflammation (Perry et al., 2020).

Finally, early case reports indicate a tendency for individuals with schizophrenia to consume an excessive amount of fluid (i.e., polydipsia; Hoskins, 1933). The rate of polydipsia that is not secondary to a medical cause in persons with schizophrenia ranges from 11-20 % (Sailer et al., 2017) and occurs in both inpatient (De Leon et al., 2002) and outpatient settings (Iftene et al., 2013). Approximately 20 % of these patients further develop the dangerous condition of hyponatremia, or water intoxication (i.e., abnormally low level of sodium in blood) as a result (Sailer et al., 2017). However, the mechanism of primary polydipsia remains poorly understood. The water balance within the body is regulated by the sense of thirst and the secretion of the hormone arginine vasopressin (Frank and Landgraf, 2008). Schizophrenia patients with polydipsia indeed show a hyp oversensitivity to vasopressin (Goldman et al., 1988) and increased secretion of vasopressin during acute psychosis (Goldman et al., 1997), which seems to be related to altered hippocampal response to stress (Goldman, 2014). On the other hand, it is inconclusive whether persons of schizophrenia have an elevated desire for water due to large variability among individuals and limited sample size (Goldman et al., 1988). Self-reported reasons behind excessive drinking include thirst, hunger, delusion, desire for intoxication, anxiety and discomfort, and for some, the reasons are unknown (Iftene et al., 2013). The role of antipsychotics remains unclear as they have been reported to both induce and improve polydipsia (see Kirino et al., 2020 for review).

2.3.5. Nociceptive system

Nociception refers to the processing of noxious stimuli, including intense chemical, mechanical, and thermal stimulation, that may lead to tissue damage. Nociceptors relay these signals to the brain mainly via spinal afferent neurons, resulting in the subjective feeling of pain. The primary somatosensory cortex processes basic features of this signal (e.g., intensity and location of noxious stimuli), while anterior insula and brainstem are involved in anticipating and paying attention to pain, as...
well as evaluating the unpleasantness of pain and related anxiety (Aziz and Ruffle, 2019).

In 1919, Kraepelin noted that “patients [with schizophrenia] often become less sensitive to bodily discomfort” (Kraepelin, 1971). A recent meta-analysis supported his observation: persons with schizophrenia report less sensitivity to noxious stimuli than healthy participants in controlled experiment settings (Stubbis et al., 2015). Specifically, they endorsed a higher threshold for pain (the point where a stimulus is experienced as painful), higher pain tolerance (the point where pain is no longer tolerable), and lower ratings of pain intensity and unpleasantness than healthy participants (Stubbis et al., 2015). Furthermore, reduced reported pain sensitivity was related to more severe clinical symptoms. Although antipsychotic medication reduces pain sensitivity (Seidel et al., 2010), unmedicated persons with schizophrenia and unaffected relatives of persons with schizophrenia (Hooley and Delgado, 2001) also report higher pain thresholds, suggesting that reduced pain sensitivity in schizophrenia is not wholly secondary to neuroleptics.

Differences in pain sensitivity reported above may reflect group differences in response bias and demand characteristics. That is, noxious stimuli may be experienced as similarly painful in individuals with and without schizophrenia, but individuals with schizophrenia may be less likely to report these stimuli as painful in a laboratory setting. Arguing against such an explanation are findings from clinical settings: the prevalence of reported clinical pain does not differ between persons with schizophrenia and healthy people (see Stubbis et al., 2014 for a review and meta-analysis), despite more physical comorbidities in persons with schizophrenia (see Leucht et al., 2007 for a review) that one would expect to lead to higher levels of pain. Furthermore, persons with schizophrenia had a lower physiological response (e.g., blood pressure change, heart rate change, withdrawal reflex) to noxious stimuli (Stubbis et al., 2015), indicating a reduced autonomic response to noxious stimuli alongside a reduced subjective experience of pain. Corroborating such an interpretation are findings that unmedicated and actively psychotic persons with schizophrenia showed over-activation of the primary somatosensory cortex, but under-activation in the posterior cingulate cortex, insula, and brainstem while enduring noxious stimuli (de la Fuente-Sandoval et al., 2010). Greater activation in the primary somatosensory cortex may reflect a higher pain threshold in individuals with schizophrenia (and hence more intense noxious stimuli endured during the experiment), and under-activation in the insula and brainstem may reflect a reduced awareness of and/or aversiveness to pain, consistent with their subjective report of lower unpleasantness of pain.

2.3.6. Thermoregulatory system

There are thermoreceptors throughout the central and peripheral nervous systems, receiving temperature signals from the brain, the skin, and oral and urogenital mucosa (Romanovsky, 2018). In response to temperature changes in the environment and/or within the body (e.g., resulting from exercise), we engage in behavioral (e.g., heat avoidance, adding clothes) and/or autonomic (e.g., sweating, skin vasodilation, shivering, and skin vasoconstriction) thermoregulatory processes. The preoptic anterior hypothalamus is considered the most important brain region for triggering autonomic thermoregulatory processes. The preoptic anterior hypothalamus is considered the most important brain region for triggering autonomic thermoregulatory processes (Romanovsky, 2018). It’s unclear what central substrates play key roles in behavioral thermoregulatory processes, but insular, cingulate, and orbitofrontal cortices are strong candidates (Craig, 2018).

There is a long history of research into thermoregulation in persons with schizophrenia. The majority of research has suggested that altered thermoregulation could be one contributor to the symptom of bizarre or redundant clothing (i.e., wearing multiple layers of clothes in warm weather). However, empirical findings supporting this hypothesis are mixed (see Chong and Castle, 2004 for review). Studies conducted in the pre-neuroleptic era (i.e., pre-1955) tended to find lower baseline temperature in persons with schizophrenia than healthy participants (Buck et al., 1950; Cameron, 1934), while later studies tended to find a higher baseline temperature in persons with schizophrenia (Madjирова et al., 1995; Morgan and Cheadle, 1976; Shiloh et al., 2000, 2001, 2003), though findings are mixed even within these earlier and later literature (see Douglas and Toogood, 1987; Freeman, 1940; Hermesh et al., 2000). There is also evidence for an impaired ability to lower body temperature within a hot environment or after exercise in persons with schizophrenia, regardless of medication status (Gottlieb and Lindner, 1935; Hermesh et al., 2000; Shiloh et al., 2001). Again, however, these findings are inconsistent across studies (Buck et al., 1951, 1950; Cameron, 1934; Douglas and Toogood, 1987; Freeman, 1940, 1939). Lastly, studies from both pre- and post-neuroleptic eras found abnormal circadian temperature variation in persons with schizophrenia (Buck et al., 1950; Denison et al., 1999; Madjирова et al., 1995; Morgan and Cheadle, 1976; but see Rao et al., 1995). Discrepant findings may be due to various factors such as methodological limitations and confounding medication effects. For example, earlier studies did not control room temperatures while participants’ baseline body temperature were repeatedly measured throughout the day, did not report the exact statistics on group differences, and employed varying methods to create heat stress. Later studies were also plagued by single-digit sample sizes, lack of control groups, and inconsistent enforcements of medication wash-out periods across studies (see Chong and Castle, 2004 for review).

There is evidence suggesting that antipsychotics may affect body temperature, which could be a factor contributing to the group difference in baseline temperature and/or the altered thermoregulation in persons with schizophrenia. In the most extreme cases, there have been reports of both hypothermia (dangerously low body temperature) and hyperthermia (dangerously high body temperature) following antipsychotic use (van Marum et al., 2007). Interestingly, animal experiments have shown that antipsychotic administration can lead to hyperthermia in cold and room-temperature environments, but hyperthermia in a hot environment (Lin et al., 1979), suggesting that antipsychotics induce such extreme body temperature conditions by impairing thermoregulatory mechanisms (Kreuzer et al., 2012; but see Mahintamani et al., 2015 for impaired thermoregulation in medication-free patients).

2.4. Summary

In summary, there is evidence suggesting altered functioning in every bodily system reviewed here in persons with schizophrenia, with some having more consistent or more direct evidence (e.g., cardiovascular, respiratory, nociceptive systems) than others (e.g., genitourinary, thermoregulatory systems), indicative of potential missteps at different stages of the interoception-allostasis process in schizophrenia (Fig. 1). Some group differences have been proven robust even after accounting for the effects of antipsychotic medications, such as reduced HRV and reduced pain threshold in persons with schizophrenia. With the exception of group differences in lung function, which persist even after taking into account medical comorbidities, there is little data from other interoceptive systems that can address the degree to which differences in bodily function in schizophrenia are attributable to primary medical conditions. In interpreting the significance of these findings, we will consider the specificity of these findings to schizophrenia and whether variability in interoception may partially account for heterogeneity in illness presentation.

Regarding specificity, some of the findings on altered bodily functioning reviewed here have been observed in other mental health conditions as well. Indeed, some researchers have argued that the experience of chronically elevated surprise about interoceptive signals may be a risk factor for many forms of psychopathology (Stephan et al., 2016), and abnormal interoception may underlie the general susceptibility to psychopathology (Murphy et al., 2017). For example, reduced HRV has been observed in anxiety disorders (see Chalmers et al., 2014 for meta-analysis), persons with major depressive disorder (Kemp et al., 2012), bipolar disorder (Critchley et al., 2019), and personality disorders (Critchley et al., 2019). However, there is preliminary evidence that reduced HRV is more pronounced in people with psychosis, compared to...
those with anxiety and depression (Critchley et al., 2019). These findings suggest that reduced HRV is not specific to schizophrenia, but cannot be completely explained by comorbid depression and anxiety symptoms either.

Lastly, the issue of illness heterogeneity has been largely ignored in most studies reviewed here. Relationships between abnormal functioning of bodily systems and clinical symptoms have been largely unexamined or examined without appropriately controlling for potential confounding factors. As reviewed above, there is some evidence that different interoceptive dysfunctions may be present in different subsets of persons with schizophrenia, but the data is too limited to yield any firm conclusions.

2.5. Integration of Interoception and exteroception

Interoception has implications for not only how we interpret our internal milieu, but also how we perceive the external world. For example, a recent study found that our brain coordinates processing internal signals and processing external signals by strategically attending to the outside world during more quiescent internal periods (indexed by the cardiac phase when the heart relaxes to fill the chambers with blood; Galvez-Pol et al., 2020). However, there is evidence that such dependence of exteroceptive sensitivity on cardiac phases is altered in individuals with schizophrenia. One study found that relative to healthy controls, persons with schizophrenia are less able to judge whether a series of auditory tones were synchronous with their heartbeat (Critchley et al., 2019). Other studies found that heartbeat modulates the perception of auditory tones (Cohen et al., 1980) and emotional faces (Critchley et al., 2019) in a different way in persons with schizophrenia, compared to healthy controls. These findings suggest potential alterations in interoceptive processing and/or the coordination of interoceptive and exteroceptive processing in persons with schizophrenia. Notably, perceptual disturbances—from subtle perceptual aberrations to vivid illusions to outright hallucinations—are prevalent in persons with schizophrenia, and have been theorized to have downstream consequences that potentially lead to altered thought processes (Maher, 1974; Silverstein, 2016). However, whether the coordination between interoception and exteroception contributes to perceptual abnormalities in the schizophrenia spectrum is unclear.

In line with these suggestions of reduced integration of interoceptive and exteroceptive signals in schizophrenia is a larger body of work describing broader alterations in multimodal sensory integration, which is crucial to integration of interoceptive and exteroceptive signals (Quigley et al., 2021). Accumulating evidence suggests that just like unimodal perception, multisensory integration is a complex inferential process where the brain weights and combines incoming signals from different sensory modalities depending on their reliability, while taking into account the uncertainty of the underlying causes (Kording et al., 2007; Rohe and Noppeney, 2015a, 2015b; Shams and Beierholm, 2010). Later, we will focus on estimates of this reliability in the form of uncertainty or precision, and how precision plays a key role in inferential processes in the brain. There is an evidence base for abnormal temporal binding (see Zhou et al., 2018 for a meta-analysis) and altered neural oscillation (Balz et al., 2016; Roa Romero et al., 2016) in multisensory processing in schizophrenia. Abnormal temporal processing of multisensory signals is further correlated with clinical symptoms (Foucher et al., 2007; Stevenson et al., 2017) and potentially abnormal self-experience (Eibisch et al., 2014; Klaver and Dijkerman, 2016; Postmes et al., 2014).

3. Interpretations through the interoceptive inference theory

This section provides a potential interpretation of the findings reviewed above through the interoceptive inference theory, a computational framework that conceptualizes interoception as hierarchical Bayesian inference. We start with a brief introduction of the theory, then provide initial conjectures regarding the mapping of interoceptive findings in schizophrenia onto specific computational terms within the model.

3.1. Interoceptive inference theory

The interoceptive inference theory is a specific implementation of Bayesian inference models of brain function, which posit that our brain maintains an internal probabilistic model of the world and makes predictions about the causes of sensory inputs (Friston, 2010; Knill and Pouget, 2004). To achieve the most accurate model possible, our brain constantly attempts to minimize mismatches between the predicted and actual state of the world. Similarly, the interoceptive inference theory posits that our brain maintains a model of the body and interprets the state of the body by weighting both expectations about bodily states and interoceptive signals (Barrett and Simmons, 2015; Seth et al., 2012; Seth and Friston, 2016). Specifically, the brain generates predictions regarding the state of the body based on past experience and current context, while the body generates bottom-up signals detailing the actual physiological state of the body at the moment. The brain’s ultimate goal is to come up with the best inference of the bodily state to maintain allostatics (i.e., predictively regulate the bodily systems to meet metabolic needs in the most energy efficient way).

Like inferences about the causes of exteroceptive input, interoceptive inference can be implemented in the brain through (Bayesian) predictive coding, a subset of Bayesian inference models (Friston, 2010; Rao and Ballard, 1999). According to this account, the brain’s goal is to minimize the mismatch between the predicted and actual bodily state (i.e., the prediction error) to achieve an accurate model of the body. In computational terms, the predictions (prior) and the sensory data (likelihood) are represented by probability distributions (Fig. 2). The prior and the likelihood are combined according to Bayes’ rule to compute the most likely inference (posterior). The posterior mean can be expressed as the combination of the prior mean and a precision-weighted prediction error signal. Specifically, the prediction error is the difference between the means of the prior and the likelihood distributions, weighted by their corresponding precisions. Precision is the inverse variance of the probability distribution, and can be understood as the reliability of the prior or sensory data. In other words, the more precise a probability distribution of prior or likelihood is, the more “weight” it has in influencing the posterior by moving the posterior mean closer to its mean.

In the case of interoception, the prior and likelihood distributions describe the desired vs. actual internal signals such as heart rate and body temperature. When the difference between the mean of the prior and the likelihood distribution is small, the brain maintains its current model of the body (i.e., the posterior equals the prior). When the difference is large, this dynamic weighing process can lead to two different strategies in minimizing the prediction error depending on the precision of the prior and the likelihood: if the precision of the likelihood is high relative to the precision of the prior, the brain is more likely to shift the prior to match the sensory data (i.e., update the model of the body); if the prior outweighs the likelihood, the brain is more likely to engage in active inference (an extension of the Bayesian predictive coding model; Friston et al., 2013) to shift the incoming sensory data towards the prior (i.e., change the sensory input through hormonal, visceral, immunological, and autonomic mechanisms or behavior; Pezzulo et al., 2015; Seth, 2015). For example, we have a very precise prior (i.e., within a small range) on ideal heart rate, so natural variations in heart rate (i.e., deviations from the prior) are constantly regulated by the autonomic nervous system.

1 There are many ways to implement Bayesian inference in the brain to understand perception and behavior (Vilares and Kording, 2011). Bayesian predictive coding is just one such computational model.
According to the Bayesian predictive coding framework, such Bayesian inference processes are situated within a hierarchical system where higher levels integrate a larger amount of information from more sources. In the context of interoceptive inference, the low-level priors map onto the functions of single organs or specific receptors (e.g., specific ranges of blood pressure, heart rate, and body temperature), while high-level priors map onto more generalized and abstract bodily states (e.g., fatigued, energetic, healthy, a general sense of malaise), and the likelihood data to be compared with high-level priors are likely integrated across multiple interoceptive systems, and sometimes may include exteroceptive information as well (e.g., visual information of room temperature or how much food is consumed). When prediction errors cannot be resolved at lower levels (e.g., through simple autonomic reflexes), then the prediction error is propagated upward through the hierarchy, requiring problem-solving at the conscious level and more integrated and/or systematic interventions like adaptive behavior (Owens et al., 2018). For example, when preparing to deliver a public presentation, your brain predicts that your body will need more energy and send out such autonomic commands to different bodily systems. At the same time, your brain also sends out predictions of potential interoceptive input as a result of the autonomic adjustments: that you may feel your heart beating faster, your face getting warmer, your hands shaking, your throat feeling dry, etc. At the conscious level, the combined pattern of these interoceptive signals may bear the name of “excited,” “anxious,” “embarrassed,” or “nervous” in different situations. The ultimate interpretation of this pattern of interoceptive signals combined over multiple sources in this particular instance depends on your higher-level prediction of your emotional state, which is heavily informed by previous situations where you have experienced similar interoceptive signals (i.e., priors at even higher levels of the processing hierarchy). As you continue to give the presentation, you may experience changes that conform or not with your predicted pattern of interoceptive signals. What you “feel” emotionally may change accordingly as well, as you incorporate new prediction errors, regulate your body differently, or shift your attention elsewhere. As your emotional state changes, you may also decide to adopt different behavioral strategies to better accommodate your allostatic needs (e.g., if you are feeling too anxious, you may decide to take a pause and drink some water to calm yourself down). In other words, emotion is a constructed concept for conscious description of the consequences of active interoceptive inference (Barrett, 2017). It is not the same as interoceptive predictions (as many of them are unconscious and too localized and specific to single organs and receptors), but a more abstract conscious “label” that enables...
us to better understand or explain our bodily state, prepare for bodily sensations, and decide on adaptive actions when in need. This dynamic updating process and the inferential nature of emotion can also explain why we may have slightly different patterns of bodily sensations for the same emotion, as well as the same pattern of bodily signals for different emotions, because emotion emerges through a dynamic process that incorporates information over multiple sources (i.e., interoception, context, past experience, attentional focus).

3.2. Bayesian predictive coding theory on integration of Interoception and exteroception

Recently, the Bayesian predictive coding framework has been applied to the integration of interoception and exteroception as well. A unified cortical hierarchy of Bayesian predictive coding has been proposed, whereby interoceptive and exteroceptive signals and prediction errors are processed separately at lower levels, but jointly at higher levels (e.g., Ainley et al., 2016; Allen and Tsakiris, 2019; Ondobaka et al., 2017; Pezzulo et al., 2015). In other words, multisensory inputs are integrated at higher levels of an inferential hierarchy, and higher-level priors determine which sources of input should be assigned more weight in a given situation. For example, Ainley and colleagues argue that individual differences in interoceptive accuracy supports the notion of a higher-level prior for bodily signals: those who are more accurate at detecting their own heartbeats are better at prioritizing interoceptive input over other sensory modalities when appropriate, potentially by assigning these bodily sensations more weight through attention modulation when it is contextually appropriate (Ainley et al., 2016). Pezzulo and colleagues proposed that all motivated behavior is the result of joint minimization of interoceptive and exteroceptive prediction errors: interoceptive prediction errors inform our brain of motivational need based on the discrepancy between current and optimal bodily states, while exteroceptive prediction errors inform our brain of the external environment in order to generate potential actions to bring our body to an ideal state (Pezzulo et al., 2015).

Other researchers hold a stronger position on the weight of interoceptive information in multisensory integration. Allen and Tsakiris argued that bodily signals are, by default, given priority (i.e., afforded greater precision) over other sensory channels because paramount goal for all organisms is to maximize their chance of survival through the interoception-allostasis process (Allen and Tsakiris, 2019). Under this premise, interoceptive signals are weighted heavily due to their high expected precision. In their model of this global predictive hierarchy, Allen and Tsakiris further proposed that at the very top of the hierarchy sits the metacognitive self-model – the brain’s prediction of its own reliability. Whenever making specific predictions, the global self-model will constrain the activities of all relevant interoceptive and exteroceptive modules, assigning more or less weight to the relevant priors and prediction errors, depending on how reliable the brain predicts information from a certain modality to be. For example, one study found that when interoceptive arousal was blocked by medication, participants became more accurate and confident on judging their own performance on a motion perception task (Hauser et al., 2017). In other words, when there is less (reliable) interoceptive information, the self-model assigns the exteroceptive signals more weight and the corresponding metacognition gains more certainty. Therefore, changes in interoception may change the certainty of our metacognition and hence our perceptions of the outside world too (Allen et al., 2019).

Although there has been limited empirical testing of Bayesian predictive coding models as they apply to interoception or the integration of interoception and exteroception, a key network supporting interoceptive inference has been proposed (Barrett and Simmons, 2015; Smith et al., 2017). The Embodied Predictive Interoceptive Coding (EPIC) model proposed a detailed account of how interoceptive predictions and prediction errors may transmit within the central nervous system (Barrett and Simmons, 2015). Within this model, agranular visceromotor cortices (including cingulate, posterior ventral medial prefrontal cortex, posterior orbitofrontal cortex, and ventral anterior insula) estimate the allostatic needs of the body, based on current resources and past experience. Accordingly, they generate autonomic, hormonal, and immunological commands to regulate corresponding systems. At the same time, these regions also send out interoceptive predictions of the expected sensations resulting from such allostatic changes over the body to the primary interoceptive sensory cortex – the mid-to-posterior insular cortex. Afferent interoceptive signals then travel up to be compared with the predicted signals, and a prediction error is computed. These prediction errors are then propagated back to the visceromotor regions where the predictions originated.

Within the EPIC model, there are three ways to minimize interoceptive prediction errors. First, the visceromotor cortices can issue new regulatory commands to the spinal cord to better meet the body’s allostatic needs and thus resulting in new interoceptive afferent inputs (i.e., active inference via overt autonomic action). Second, the visceromotor cortices can send new interoceptive predictions to the mid-to-posterior insular so that they may better match with the incoming interoceptive signals (i.e., belief updating). Third, the anterior insula and the anterior cingulate cortex can change the focus of attention and adjust the sampling or processing of the interoceptive signals to better match with the prediction (i.e., active inference via covert attentional action).

3.3. Implications for interoception findings in schizophrenia

The literature reviewed here suggests that altered interoceptive functioning may be present in various bodily systems in persons with schizophrenia. As a first step towards developing a comprehensive mechanistic understanding of these findings, we will interpret them through the lens of interoceptive inference theory. Within the computational framework of Bayesian predictive coding, altered interoceptive inference may be caused by alterations in one or more model parameters: (1) biased prediction error signals due to altered precision of priors and interoceptive signals (i.e., imbalanced precision weighing of the two probabilistic distributions, see Figures 2B & 2C), (2) biased priors (i.e., a shifted mean of the prior distribution, see Fig. 2E), and (3) unsuccessful minimization of prediction error signals due to dysfunction in autonomic regulation (i.e., errors in the execution, rather than inferential, steps of active inference).

Though alterations in different processes that map on to the aforementioned computational terms may lead to the same clinical phenomenon, it is nevertheless important to pinpoint the exact problem, as different mechanisms of interoceptive alterations may call for very different interventions. Specifically, (1) altered precision of priors and interoceptive signals may lead to overweighting priors or prediction errors in contexts where they ought not be. Hyperprecise priors relative to prediction errors will bias the posterior inference towards the prior and stymie model updating, thus leading to a rigid model of the body that is resistant to feedback from bodily signals (Fig. 2B). This may manifest as a slow or attenuated response to changes in interoceptive signals, or a rigid behavioral pattern that is maintained despite changes in metabolic needs. On the other hand, hyperprecise prediction errors relative to priors may lead to an unstable model of the body that is updated too frequently, and thus leading to maladaptive behavior that does not maintain allostatic (Fig. 2C). This may manifest as idiosyncratic and rapid changes in regulation of the body that are not consistent with environmental changes and/or metabolic needs. (2) Biased priors will lead to a chronically inaccurate posterior inference and, thus, long-term homeostatic imbalance (Fig. 2E). Observationally, this may manifest as a difference in baseline bodily state between persons with schizophrenia and healthy individuals. (3) Dysfunctions in autonomic regulation may lead to impaired ability to minimize interoceptive prediction errors through autonomic mechanisms. This may manifest as reduced autonomic regulation and increased compensatory use of (seemingly excessive) behavioral regulation to address anticipated metabolic needs.
However, persistent reductions in autonomic regulation may lead to a chronic homeostatic imbalance as a biased prior would. Therefore, it could be difficult to differentiate these two underlying mechanisms without directly manipulating one or the other.

In attempting to interpret data from individuals with schizophrenia in relation to the above hypotheses, we operated under the following assumptions: chronic, static, or baseline differences in bodily states likely reflect a biased prior and/or chronic autonomic dysregulation (that fails to restore homeostasis); differences in temporary, situational, or dynamic changes in bodily states likely reflect more transient autonomic dysregulation or alterations in precision weighting of priors and likelihood (that leads to an altered response, or lack thereof, to homeostatic challenges). Evidence consistent with hyperprecise priors relative to likelihood include reduced sensitivity to changes in the amount of food one has consumed and lower oxygen uptake during exercise in persons with schizophrenia. Evidence suggesting reduced autonomic regulation include higher risk of urinary incontinence and higher rate of childhood enuresis in persons with schizophrenia. Other findings may reflect either altered precision weighting or autonomic dysregulation, such as reduced heart rate variability, increased rate of primary polydipsia, and alterations in circadian temperature variation and thermoregulation in persons with schizophrenia, as well as decreased synchrony between heart rate and respiration in unmedicated patients. For biased priors, consistent evidence includes increased baseline heart rate, restricted lung function at rest, and alterations in baseline body temperature in persons with schizophrenia, as well as increased baseline breathing rate and increased tachygastria in stomach in unmedicated patients. Lastly, reduced pain sensitivity may indicate either a hyperprecise prior (of “not in pain”) or a biased prior (that includes low intensity pain in its distribution).

It is worth pointing out that the aforementioned hypotheses regarding interoceptive inference dysfunction within the Bayesian predictive coding framework are not mutually exclusive. For example, reduced autonomic regulation is equally likely a result of imprecise interoceptive signals (that will not trigger active inference) or problems within the central and/or peripheral autonomic nervous system (that lead to suboptimal autonomic commands). In fact, some mechanisms may even lead to the development of alterations in other processes. For instance, altered precision modulation or autonomic dysregulation may lead to chronically elevated prediction errors (that may or may not reflect a true deviation from homeostasis), which may in turn bias the lead to chronically elevated prediction errors (that may or may not lead to suboptimal autonomic commands). In fact, some mechanisms that have been posited to play a key role in precision modulation (e.g., norepinephrine, acetylcholine, and dopamine; Smith et al., 2017). Additionally, medical comorbidities may lead to imprecise interoceptive signals and autonomic dysregulation. For example, there is a high rate of Type II diabetes among individuals with schizophrenia (Laursen et al., 2014). Nerve damage is secondary to insulin dysregulation, which will result in imprecise (or even absent) interoceptive signals such as numbness in extremities.

4. An integrated bayesian predictive coding account of schizophrenia

In this section, we will provide a possible account of how alterations in interoceptive inference may contribute to the clinical presentation of schizophrenia generally, and to negative symptoms in particular. We begin by briefly reviewing existing Bayesian predictive coding accounts of schizophrenia symptoms (mainly positive symptoms) and extending the account by integrating interoceptive inference into the framework. Next, we introduce an existing interoceptive inference model of depression and propose that a similar model may have explanatory power for motivational negative symptoms in schizophrenia.

4.1. Interoceptive inference and positive symptoms

The Bayesian predictive coding account of schizophrenia has been primarily applied to exteroceptive perception and accounts for positive symptoms in particular (Corlett et al., 2016; Fletcher and Frith, 2009; Sterzer et al., 2018). Such theories argue that hallucinations and delusions result from an imbalance in the weighting of priors and sensory data. In other words, aberrant encoding of uncertainty or precision may lead to false inferences in the form of hallucinations (i.e., inferring things are there when they are not; Adams et al., 2013). Specifically, two different mechanisms have been proposed and both have received some empirical support: hypoprecise priors relative to sensory data (see Notredame et al., 2014; Thakkar et al., 2017; van Lutterveld et al., 2011 for review) and hyperprecise priors relative to sensory data (see Corlett et al., 2019 for review). This apparent discrepancy has been argued to stem from differences in the weighting of priors and sensory data across a processing hierarchy (Corlett et al., 2019) and, relatively, differences in the degree to which specific priors are constrained by the information processing system (Teufel and Fletcher, 2020).

Now, the Bayesian predictive coding theory suggests that precision can be operationalized as the excitability, or gain, of neuronal populations encoding prediction errors at various levels in the cortical hierarchy (Feldman and Friston, 2010; Friston, 2008). This provides a common mechanism underlying attention and sensory attenuation - increases in sensory precision may be related with selective attention, while decreases in sensory precision may be related with sensory attenuation. It has been widely replicated that persons with schizophrenia do not properly attenuate sensory precision while executing self-generated actions (reviewed in Bansal et al., 2018; Feinberg and Guazzelli, 1999; Ford and Mathalon, 2004; Thakkar et al., 2017). Consequently, there may be a compensatory increase in prior precision, which may then lead to the development of positive symptoms (Corlett et al., 2019).

We underscore the relevance of altered precision modulation in schizophrenia as the same principles may apply to interoceptive inference and similarly lead to positive symptom development. Mechanistically, if interoceptive prediction errors are not attenuated, they will lead to belief updating at the expense of active inference. In other words, altered precision control would have the dual effect of compromising autonomic reactivity (e.g., reduced HRV, decreased synchrony between heart rate and respiration, and altered thermoregulation in persons with schizophrenia) while, at the same time, promoting belief updating at higher cortical levels (e.g., the formation of somatic delusions and agency disturbances). The compensatory increase in prior precision may manifest as reduced sensitivity to interoceptive afferents (e.g., reduced sensitivity to changes in the amount of food one has consumed in persons with schizophrenia).

Furthermore, we would like to propose that altered interoceptive inference and unbalanced interoception-exteroception integration may be particularly relevant at the prodromal stage of the illness, in a manner similar to what has been proposed to explain chronic anxiety. Specifically, the somatic error hypothesis of anxiety proposes that maladaptive attempts to resolve frequently elevated interoceptive prediction errors...
may lead to chronic anxiety, manifesting as self-related thinking patterns and a preoccupation with and hypervigilance towards bodily signals (Khalsa and Feinstein, 2019; Paulus et al., 2019). Likewise, in persons with schizophrenia, a chronically elevated low-grade arousal state (indexed by increased heart rate and reduced HRV) could lead to frequent interoceptive prediction errors and a vague sense that “something doesn’t feel right.” However, unlike persons with primary anxiety symptoms who have highly precise interoceptive signals (indexed by superior interoceptive accuracy; see Domschke et al., 2010) for review), individuals with schizophrenia seem to have imprecise interoceptive signals (indexed by poor cardiac interoceptive accuracy). Consequently, the brain may decide that interoceptive signals are unreliable in general and down weight the interoceptive modality as a whole in multisensory integration. As a result, exteroceptive signals are assigned more precision (than they should have) and end up biasing the eventual inference towards the exteroceptive modality. In other words, prediction errors may be reconciled through an updating of the world model, rather than of the bodily state model. Over time, this may become what Conrad termed a “delusional mood” - a global and permeating feeling of something important impending, or that “something is in the air” (Mishara, 2010). Propelled by the need to discover the cause for this delusional mood so that interoceptive prediction errors can be resolved and homeostasis can be re-established, the central nervous system may enhance the processing of exteroceptive information (i.e., a preoccupation with and hypervigilance towards any external stimuli that may be a “clue”). Consequently, external stimuli become more salient and “meaningful,” feeding into an inference about the external world that may become increasingly divorced from consensual reality. Under the influence of the strong prior that “something is in the air,” noisy exteroceptive signals may be unduly influenced by this prior, resulting in an expectancy that engenders hallucinations (Corlett et al., 2019; Hoffman, 2010; Leptourgus and Corlett, 2020). These hallucinations then feed back into the processing loop as evidence for the delusional prior (that something important is impending). Eventually, this process of circular inference (Jardri and Denève, 2013) crystallizes into elaborate delusions that are so precise that even obvious contradictory evidence cannot budge them. Supporting such an argument are studies showing the prevalence of bodily feelings co-occurring with hallucinations in early psychosis (Melvin et al., 2021), a close temporal association between momentary autonomic arousal and increase in auditory hallucinations (Kimhy et al., 2017), as well as a correlation between an elevated low-grade arousal state (indexed by reduced HRV over an 8-h period) and more severe positive symptoms (Cella et al., 2018). Other studies have found that insula and adjacent brain regions activate a few seconds before and during auditory hallucinations (see Zmigrod et al., 2016 for a meta-analysis; also see Hoffman et al., 2008; Powers et al., 2017), linking the key interoceptive hub with hallucinations. A recent simulation study also found that subjects with imprecise interoceptive signals demonstrate overly precise priors for visual perception, further intimating a link between disrupted interoceptive precision and hallucinations (Allen et al., 2019).

4.2. Interoceptive inference and negative symptoms

Given the phenomenological overlap between some of core motivational negative symptoms and depression (e.g., anhedonia, reduced level of activity), some existing interoceptive inference models of depression may have explanatory power for negative symptoms as well (Barrett et al., 2016; Chekroud, 2015; Schutter, 2016; Seth and Frisson, 2016; Stephan et al., 2016). Stephan and colleagues proposed that depression may be a metacognitive response to chronically elevated interoceptive prediction errors (Stephan et al., 2016). Chronically elevated interoceptive prediction errors present a warning signal to the brain that it cannot regulate bodily states adequately for survival. As an adaptive response to preserve more energy and re-establish homeostasis, the brain shifts to a sickness motivational state and initiates a repertoire of sickness behavior: fatigue, anhedonia, irritability, fragmented sleep, reduced calorie and fluids intake, reduced level of activity, and social isolation (all symptoms of depression). However, because the interoceptive prediction errors were not due to a true deviation from a healthy bodily state, engaging in sickness behavior cannot successfully restore homeostasis and may even push the bodily state towards further dysregulation. Over time, this low allostatic self-efficacy (a perceived lack of control over bodily states) may become a generalized sense of low self-efficacy – the hallmark defeatist beliefs in depression. Although proposed as an explanation for depression, the authors argue that low self-efficacy induced by chronically elevated interoceptive prediction errors may be a more general marker of reduced resilience to stress, and thus a risk factor for many different forms of psychopathology.

Accordingly, it follows that motivational negative symptoms may also be a response to a perceived lack of control over one’s own bodily states and defeatist beliefs in general (Grant and Beck, 2009), given the prototypical overlap between negative symptoms and sickness behavior (i.e., fatigue, anhedonia, reduced level of activity, and social isolation) and the growing evidence of immune dysfunction in persons with schizophrenia (Miller and Goldsmith, 2017; Pruessner et al., 2017; Severance et al., 2012). Various mechanisms may lead to chronically elevated interoceptive prediction errors: altered interoceptive signals (due to dysfunction in organs, receptors, the vagus nerve, and/or the insula), altered interoceptive priors (due to dysfunction in visceromotor regions), or autonomic dysregulation (due to dysfunction in central or peripheral autonomic nervous system; Stephan et al., 2016). Barrett and colleagues proposed that inaccurate precision signaling of prediction errors may be another potential mechanism leading to chronically elevated interoceptive prediction errors (Barrett et al., 2016). As demonstrated in previous sections, the wide range of putative alterations in interoceptive systems in schizophrenia point to potential dysfunction in all of these mechanisms.

Nevertheless, chronically elevated interoceptive prediction errors is not the only route that could lead to negative symptoms. Stephan and colleagues proposed that the onset of sickness behavior can result from prediction errors broadly, not just interoceptive prediction errors, that cannot be reconciled by actions, which will then inevitably lead to the same sense of lack of control (Stephan et al., 2016). This brings up the possibility that negative symptoms may emerge simultaneously or even shortly before positive symptoms from similar alterations in Bayesian predictive coding mechanisms. Alternatively, they may develop as compensatory processes in response to initial pronoal mechanisms that give rise to positive symptoms, an idea alluded to in previous Bayesian predictive coding accounts of psychosis (Corlett et al., 2016; Fletcher and Frith, 2009). For example, the perceptual disturbances experienced by persons with schizophrenia, even before formal illness onset, can be seen as unsuccessful attempts in resolving exteroceptive prediction errors that do not lend themselves easily to rational explanation. To reduce this unpleasant sense of lack of control, the brain may resort to the strategy of reduced activity and social involvement as an adaptive attempt to minimize prediction errors, preserve energy, and maintain homeostasis (Fabry, 2020). Lastly, Jeganathan and Breakspear proposed that imprecise priors about social consequences resulting from one’s emotional behavior may lead to blunted affect, and social withdrawal in the long run (Jeganathan and Breakspear, 2021).

5. Future directions

We believe that the account outlined above, which aims to integrate interoception and exteroception into Bayesian predictive accounts of schizophrenia symptoms, provides a framework for empirical inquiry. It provides a putative computational framework that bridges behavior, cognition, and biology, with explanatory power for both negative and positive symptoms. More broadly, the current review emphasizes the importance of understanding brain-body interactions in schizophrenia. In this final section, we highlight future directions that may enable us to
better understand these brain-body interactions and their relevance for clinical symptoms and subjective experience in schizophrenia, to refine a computational account of putative interoceptive inference abnormalities, and to explore if and how such an understanding of brain-body interactions may unveil new avenues of treatment.

The first, and arguably most important, avenue for future research is to gather more direct empirical evidence that speaks to interoceptive abnormalities across modalities in individuals with schizophrenia. To date, direct research on interoception has focused almost exclusively on the cardiac system (see Khalsa and Lapidus, 2016 for review and example studies). However, interoception involves many different organs and a vast peripheral nervous system, and different patterns of relationships between interoceptive measures have been reported across modalities (Garfinkel et al., 2016; Herbert et al., 2012). Therefore, it would be unwise to focus research efforts exclusively on one model interoceptive system and assume that findings would translate to other systems. Ideally, studies should examine different interoceptive systems together instead of in isolation, since the systems may interact with one another in the dynamic process of interoceptive inference and eventually all contribute to the higher-level abstract sense of bodily state. Likewise, alterations in specific interoceptive measures and bodily systems may contribute to different clinical symptoms. For example, different indices of altered heart rate modulation in persons with schizophrenia have been shown to relate to a wide range of different symptoms (Cella et al., 2018; Kimby et al., 2017; Mathewson et al., 2012). This speaks to the importance of using multiple methods to capture all possible aspects of a single interoceptive modality rather than relying on a single paradigm (e.g., the heartbeat counting task).

Given the lack of clarity in current literature on the correspondence between observational interoceptive abnormalities in schizophrenia and the underlying computational inferential mechanisms, future work would benefit from carefully designed experiments guided by specific falsifiable hypotheses to tease apart the potential mechanisms, namely (1) altered precision modulation of priors and interoceptive signals, (2) biased priors, and (3) unsuccessful minimization of prediction errors due to autonomic dysregulation. For example, one way to separate biased priors from imprecise interoceptive signals is to take a rigorous psychophysiology approach so that the influence of response bias (i.e., a biased prior) vs. sensitivity to stimulus intensity (i.e., precision of interoceptive signals) can be quantified separately (e.g., Van Den Houte et al., 2021). Though it is much harder to manipulate interoceptive than exteroceptive signals in a non-invasive and precisely controlled manner, researchers have developed creative solutions, such as inducing changes in satiety through water or liquid food ingestion (Schulz et al., 2017; Waltz et al., 2015) and inducing changes in the sensations of breathing through manipulations of breathing load (Kruschwitz et al., 2019; Paulus et al., 2012; Van Den Houte et al., 2021) or breathing rate (Farb and Logie, 2019; Schulz et al., 2016). Such precise and controlled manipulation could enable us to establish the “ground truth” of incoming interoceptive signals, and thus obtain an objective measure of participants’ sensitivity to stimulus intensity.

One may also test altered precision modulation of priors by explicitly manipulating the probability distribution of priors through different experimental conditions. For example, when one is hungry, the anticipated bodily state after consuming a milkshake should cover a relatively wide range of probability – one can remain hungry, feel full, or feel somewhere in between. On the other hand, when one is already almost full, the anticipated bodily state after consuming a milkshake should be rather precise – it is almost certain that one should feel satiated and rather unlikely that one will feel hungry again. Therefore, the allostatic system should prepare the body accordingly, and this difference should be reflected in physiology and/or behavior (e.g., in the latter case, hunger signals should be significantly suppressed and participants should display a reduced preference for high-calorie food (Kruschwitz et al., 2019)). Similar experimental manipulations could be applied to the uncertainty around how exhausting certain exercise may be, how painful certain stimuli may be (Ploghaus et al., 2003), how likely one is sick (Constantinou et al., 2013), etc.

To examine potential altered precision modulation of interoceptive signals in persons with schizophrenia, researchers may examine the effect of attention modulation on interoceptive processes (Barrett and Simmons, 2015). For example, a promising neural index of interoceptive processing is the heartbeat evoked potential (HEP) - the neural response to heartbeat measured by electroencephalography (EEG), regardless of whether the heartbeat is consciously perceived or not (Coll et al., 2021). Recent studies have shown that the HEP is significantly larger when participants are instructed to pay attention to their heartbeats compared to when they are instructed to pay attention to external auditory stimuli (Garcia-Cordero et al., 2017; Petzschner et al., 2019), supporting the hypothesis that attention could modulate how much weight is assigned to a specific channel of information (in this case, prioritizing heartbeat sensations over auditory input when explicitly asked to do so). Future studies could use such attention manipulations and measure changes in HEP to quantitatively examine precision modulation of interoceptive signals in persons with schizophrenia.

Further research should also investigate the relationship between interoceptive abnormalities and clinical symptoms, taking into account illness development, secondary symptoms, and compensatory processes. Persons with schizophrenia often have clinically significant anxiety and depression symptoms, which may have different relationships with interoceptive functioning. For example, the relationship between interoceptive accuracy and anxious arousal is moderated by levels of anhedonia (Dunn et al., 2010), suggesting that interoceptive inference could be very different in individuals with schizophrenia experiencing high versus low levels of motivational negative symptoms and anxiety. Therefore, it will be important to broadly assess clinical symptoms when studying interoceptive inference in schizophrenia. Alternatively, using a trans-diagnostic approach to studying interoceptive inference can also help elucidate the issue of symptom specificity (e.g., Critchley et al., 2019). Relatedly, the developmental trajectory of altered interoceptive inferential processes and clinical symptoms, as well as potential compensatory strategies, may look very different from one individual to the next. Therefore, longitudinal studies that track individuals with schizophrenia across illness stages will be critical to teasing apart the undoubtedly complicated interactions among different symptoms and their underlying computational and biological mechanisms.

In addition, understanding the mechanisms of interoceptive inference in schizophrenia may provide inroads for developing novel interventions. Existing evidence-based treatments that directly or partially address interoception include: medications modulating interoceptive physiology, interoceptive exposure therapy (e.g., Meuret et al., 2018), and mindfulness-based therapy. Most evidence of treatment-related physiological and/or interoceptive changes comes from the mindfulness literature (Boccia et al., 2015; Bornemann and Singer, 2017; Delgado-Pastor et al., 2015; Ditto et al., 2006; Krygier et al., 2013; Wu and Lo, 2008), and there is growing evidence that mindfulness-based interventions are safe and effective for persons with schizophrenia (Alvarez-Jimenez et al., 2018; Hodann-Caudefilla et al., 2020; Vignaud et al., 2019), but more research is needed given the heterogeneity of interventions and methodological limitations of existing studies (Hodann-Caudefilla et al., 2020). Note that a foundational component of mindfulness-based intervention is the training of control over attentional set. Within the active inference framework, this addresses the skill of deploying different priors at different levels of hierarchical processing (or the mentalization of homeostasis, Fotopoulou and Tsakiris, 2017). Meanwhile, researchers have been developing novel interoception-based interventions aimed at improving perception of interoceptive signals, such as heartbeat perception training (Schafer et al., 2014) and intuitive eating (using hunger and satiety cues to regulate food intake; see Cadena-Schlam and López-Guimerà, 2015 for review). Other novel interoception-based interventions targeting anxiety and depression involve directly changing physiological sensations.
for a short period. Floatation-Reduced Environmental Stimulation Therapy (REST) minimizes extreroceptive sensory input to the brain while enhancing awareness and attention to cardiorespiratory sensations through floating participants in a pool of water (Feinstein et al., 2018). Whole-body hyperthermia (WBH) temporarily alters participants’ experience of bodily sensations through heating participants at the chest level and lower extremities (Jansen et al., 2016). Further research is needed to evaluate whether persons on the schizophrenia spectrum will benefit from these developing interoception-based interventions. Better understanding of various neurotransmitters’ roles in modulating the precision of priors and prediction errors in interoceptive inference may also help develop more targeted pharmacological interventions for the disorder.

Lastly, it is worth highlighting again the complicated nature of studying interoceptive functioning in schizophrenia due to factors including but not limited to: side effects of medications, prevalent medical comorbidities, and the profound mental, physical, and social consequences of living with a chronic severe mental illness with limited resources. Therefore, it will be important to disentangle secondary consequences of the illness from primary illness mechanisms.

6. Conclusions

In summary, this review contains two main contributions. First, we reviewed alterations in the bodily processes that may bear on interoception in individuals with schizophrenia and interpreted the findings through the interoceptive inference framework. Second, we proposed an integrated Bayesian predictive coding account of schizophrenia that bridges the interoceptive and exteroceptive domains, with implications for a wide range of clinical symptoms. Although this framework likely generates more questions than answers, we hope that it will provide a ground for precise theory-driven hypothesis testing that can further our understanding of the disease mechanisms of schizophrenia and eventually lead to developments of more targeted novel interventions.

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Declaration of Competing Interest

The authors report no declarations of interest.

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