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Dysregulation of auditory neuroplasticity in schizophrenia

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ABSTRACT

Schizophrenia is a complex brain syndrome characterized by an array of positive symptoms (delusions, hallucinations, disorganized speech), negative symptoms (alogia, apathy, avolition) and cognitive impairments (memory, executive functions). Although investigations of the cognitive deficits in schizophrenia have primarily concentrated on disturbances affecting higher-order cognitive processes, there is an increasing realization that schizophrenia also affects early sensory processing, which might, in fact, play a significant role in the development of higher-order cognitive impairments. Recent evidence suggests that many of these early sensory processing impairments possibly arise from a dysregulation of plasticity regulators in schizophrenia, resulting in either reduced plasticity or excessive unregulated plasticity. The purpose of the present manuscript is to provide a concise overview of how the dysregulation of cortical plasticity mechanisms contributes to schizophrenia symptoms with an emphasis on auditory dysplasticity and to discuss its relevance for treatment outcomes. The idea that plasticity mechanisms are not constrained only within sensitive periods suggests that many functional properties of sensory neurons can be altered throughout the lifetime.

1. Schizophrenia and associated sensory dysfunctions

Although traditional cognitive models of schizophrenia have concentrated on disturbances affecting higher-order cognitive abilities that include working memory and various executive functions, there is a growing awareness that such impairments are apparent even at the level of early sensory processing (see Javitt and Freedman, 2015). Although these deficits affect primarily auditory processing (see Javitt and Sweet, 2015), a growing body of evidence also points to impairments affecting the visual (Schneider et al., 2006; Revheim et al., 2006; Klosterkötter et al., 2008), tactile (Teale et al., 2013; Huang et al., 2010), and olfactory (Turetsky et al., 2009; Moberg et al., 2014) systems. Critically, most sensory dysfunctions in schizophrenia tend to go undetected unless specifically evaluated. It is imperative, however, that clinicians start monitoring auditory function. Support for such a claim is provided by a recent large cross-sectional cohort study demonstrating that early auditory information processing deficits lead to poor functional outcome via impaired cognition (Thomas et al., 2017).

Individuals with schizophrenia generally do not show deficits during routine hearing tests and brain-stem recordings, suggesting that peripheral sound processing mechanisms are likely preserved (Javitt, 2009). In contrast, individuals with schizophrenia typically exhibit higher-order auditory deficits, including elevated thresholds when performing tone-matching tasks (Rabinowicz et al., 2000). Individuals with schizophrenia also exhibit deficient mismatch negativity (MMN) event-related potentials in response to a wide variety of auditory inputs (Hay et al., 2015). The MMN is a negative event-related potential shift elicited by an unexpected deviant stimulus presented in a sequence of similar, anticipated stimuli. It is a pre-attentive process, meaning that it is observable even when individuals are not actively attending the stimuli (Näätänen et al., 2007). In fact, in persons at high clinical risk for schizophrenia, the MMN has emerged as a predictor of who will progress to schizophrenia (Perez et al., 2014). Deficits in MMN generation have also been linked with basic tone matching (Javitt, 2009) and auditory spatial impairments (Perrin et al., 2010), both underappreciated clinical features of schizophrenia (Javitt and Freedman, 2015).

Tone matching deficits also produce significant bottom-up effects in individuals with schizophrenia by affecting their capacity to detect information relating emotional prosody (Leitman et al., 2005) and sarcasm (Kantrowitz et al., 2014a). Furthermore, whereas approximately 10% of the general population exhibits musical perception deficits (Sloboda et al., 2005), the rate of similar deficits observed in schizophrenia patients is nearly fivefold (Kantrowitz et al., 2014b). The P50 evoked potential is another important measure of auditory processing that appears to be disrupted in schizophrenia. The P50 is an early positive electroencephalographic wave that occurs approximately 50 ms after stimulus onset that is often used to study inhibitory sensory gating mechanisms (Adler et al., 1982). Typically, when pairs of tones are presented, the P50 in response to the second tone is reduced, which is interpreted as evidence of neural gating. In schizophrenia, however, this attenuation is markedly impaired (Olincy et al., 2010; Patterson et al., 2008). Furthermore, P50 inhibitory gating impairments in

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schizophrenia have also been linked with the occurrence and intensity of auditory hallucinations, in addition to decreased attentional abilities (Cullum et al., 1993; Smith et al., 2010; Smith et al., 2013; Faugère et al., 2016). In fact, it has been suggested that the P50 response might represent one of the most powerful and reliable biomarkers for schizophrenia (Heinrichs, 2004).

Questions remain regarding the emergence of these auditory deficits over time. Although it remains unclear to what extent these deficits follow a similar time-course to other schizophrenia symptoms—or rather, if they are present prior to the disorder onset and contribute to its emergence—mounting evidence suggests an early emergence of these auditory impairments. In particular, altered neurophysiological mechanisms of auditory processing, as measured with EEG, have been observed in early illness schizophrenia-spectrum patients, prior to the onset of psychosis, as well as in at-risk patients (Hay et al., 2015; Perez et al., 2013; Perez et al., 2014). These findings and others suggest that such auditory electrophysiological markers could potentially be used as a diagnostic aid when assessing at-risk patients. Future research might benefit from investigating the potential diagnostic value of other key biomarkers of auditory function.

A growing body of evidence suggests that many of these early sensory processing impairments likely arise from a dysregulation of plasticity regulators in schizophrenia. The following section examines how the various plasticity regulators are affected in schizophrenia, and how their dysfunction often results in unstable and unregulated plasticity processes.

2. Dysregulation of cortical plasticity in schizophrenia

Brain plasticity (or neuroplasticity) refers to the brain's ability to adapt both structural and functional neural properties in response to internal or external stimuli (Pascual-Leone et al., 2005). Plasticity can have short-term or long-term effects (see Fig. 1, panels A and B). Short-term plasticity, also often referred to as synaptic plasticity, comprises rapid synaptic processes that operate on very short timescales to modulate synaptic efficacy and strength in an activity-dependent manner (Fioravante and Regehr, 2011). Short-term plasticity has noted effects on sensory processing and evoked electrophysiological responses, and is believed to underlie MMN generation deficits (Baldeweg and Hirsch, 2015; Näätänen et al., 2015). In contrast, long-term plasticity is viewed as the ensemble of experience-dependent mechanisms that modify neural circuits and lead to persistent modifications in the structure or functioning of cortical networks; these include long-term depression (LTD) and long-term potentiation (LTP), which produce changes in synaptic efficacy lasting hours or longer. Consequently, long-term plasticity mechanisms are viewed as the major cellular substrate for learning, memory, and behavioral adaptation (Yang and Calakos, 2013; Kandel, 2001; Granger and Nicoll, 2013). Importantly, neuromodulation can interact with plasticity mechanisms to lower the threshold for plasticity and enhance LTP (Andersen et al., 2017). Since several neuromodulatory systems are disrupted in schizophrenia, this could contribute to excessive long-term plasticity in the disease. Long-term dysplastic processes in schizophrenia are believed to underlie more chronic symptoms such as auditory verbal hallucinations (Allen et al., 2008; van Swam et al., 2012), not unlike the mechanisms believed to underlie phantom percepts in individuals with tinnitus.

Such plastic changes typically occur in one of two developmental contexts (see Fig. 1, panel C). Early developmental sensory experience can shape neuronal response properties even when an organism is not paying attention to external stimuli, a type of plasticity known as *experience-expectant neuroplasticity* (Hubel and Wiesel, 1959; Wiesel et al., 1963; Knudsen, 2004), and generally occurs within a specific time window referred to as a critical period (CP). In contrast, *experience-dependent neuroplasticity* (Klintsova and Greenough, 1999) is a form of brain plasticity that occurs throughout the lifespan and involves changes in neuronal activity induced by specific and attended

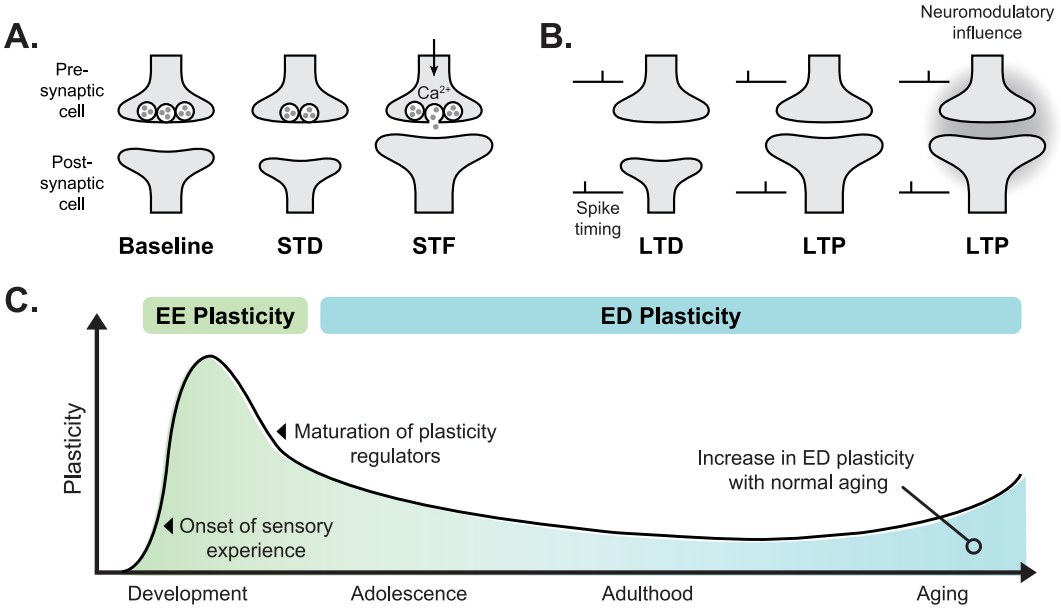

Fig. 1. Types of plasticity. A. Short-term plasticity is a rapid synaptic process that operates on a timescale of seconds. Synaptic efficacy (represented by bouton size) is temporarily weakened (Short-term depression [STD]) or strengthened (Short-term facilitation [STF]) based on recent presynaptic activity. In STD, this is primarily caused by neurotransmitter depletion, while in STF this is caused by an influx of calcium that increases the probability of neurotransmitter release. Without sustained presynaptic activity, short-term alterations will return to baseline. B. Long-term depression (LTD) and long-term potentiation (LTP) are changes in synaptic efficacy lasting hours or longer that lead to persistent modifications in the structure or functioning of cortical networks. The exact mechanisms of LTD and LTP can differ based on the brain region, but both depend on the timing of spikes between pre- and post-synaptic cells (insets). Importantly, this process can be modified by the presence of neuromodulators to promote LTP. C. Short and long-term plastic mechanisms contribute to the quality and quantity of sensory plasticity, which changes throughout the lifetime. Early life is characterized by experience-expectant (EE) plasticity, in which passive sensory experience can shape neuronal responses properties. The onset of sensory experience triggers developmental critical periods, the end of which coincides with the maturation of plasticity regulators. After maturation, experience-dependent (ED) plasticity occurs throughout the lifetime in response to specific and attended sensory experiences, which produce long-lasting changes in neural representations. This type of plasticity is dysregulated in disorders of plasticity such as schizophrenia and with aging.

sensory experiences, which produce robust and lasting changes in neural representations.

Near the end of the CP, the stabilization of sensory representations is achieved via the maturation and maintenance of inhibitory (GABAergic) cellular networks throughout the brain (de Villers-Sidani et al., 2007; Hensch, 2005; Fritschy and Panzanelli, 2014; Zhang et al., 2002). Subsequently, cortical plasticity following the CP closure is then regulated by an ensemble of plasticity inhibitors and molecular brakes (see Bavelier et al., 2010; Hensch, 2005). Such elements include the inhibitory activity provided by GABAergic parvalbumin positive (PV+) interneurons (Kuhlman et al., 2013), and the structural barriers provided by extracellular matrix components including perineuronal nets (PNNs) (Wang and Fawcett, 2012), and myelin-associated proteins (McGee et al., 2005). These brakes can be manipulated in the adult brain and CP-like plastic remodeling can therefore be achieved via the down-regulation of cortical inhibition (Fagiolini and Hensch, 2000), the disruption of PNNs (McRae et al., 2007; Wang and Fawcett, 2012; Pizzorusso, 2002), or by affecting myelin content (Kartje et al., 1999; McGee et al., 2005). Various neuromodulatory systems can also influence CPs and brain plasticity through various processes that include increasing neuronal excitability and improving the signal to noise ratio (Kirkwood, 2007). These include dopamine, norepinephrine, acetylcholine, and serotonin, all of which play important roles in gating cortical plasticity. The direct stimulation or the chemical boosting of these systems has been shown to shape cortical sensory function and affect learning rates (Bao et al., 2001; Kilgard and Merzenich, 1998; Kang and Vaucher, 2009; Noudoost and Moore, 2011; Voss et al., 2016).

The clinical syndrome of schizophrenia is characterized by alterations of brain function and plasticity. Although glutamatergic (Javitt, 2012), GABAergic (Lewis et al., 2005) and dopaminergic (Howes and Kapur, 2009) models of schizophrenia have been put forward, the picture is in reality much more complex, and the disorder is likely the result of an interplay between multiple dysfunctional neurotransmitter systems. Furthermore, many of the cardinal features of schizophrenia likely arise from a dysregulation of plasticity regulators (Keshavan et al., 2015; see also Fig. 2), with possible variations in this dysregulation occurring as a facet of the developmental course of the disorder; e.g., excessive plasticity during the initial acute psychotic episode, followed by decreased plasticity during chronic phases of the illness.

The GABAergic interneuron subset that has so far been the most related to schizophrenia is the PV inhibitory interneuron (Woo, 2014; Morishita et al., 2015). Molecular alterations in PV interneurons have

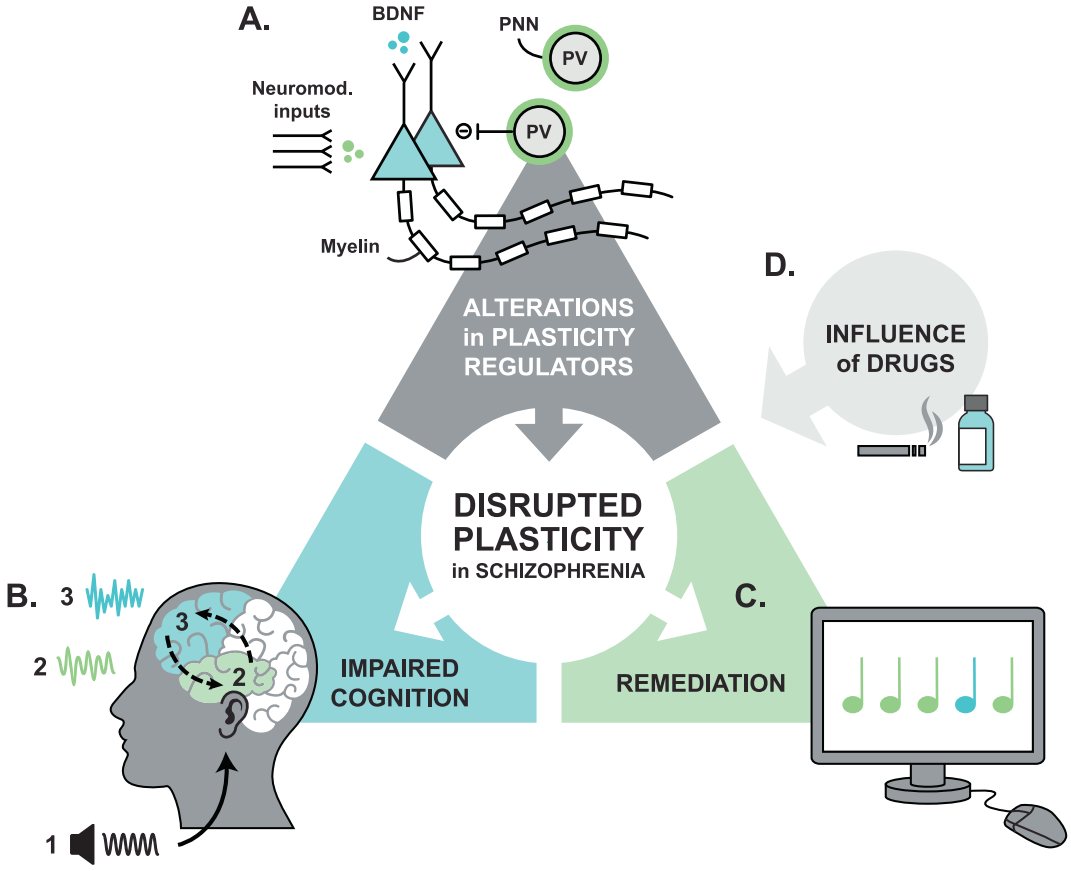

Fig. 2. Factors influencing dysregulated neuroplasticity in schizophrenia. A. Various molecular, cellular, and structural regulators of plasticity have been found to be disrupted in schizophrenia. Several inhibitory elements, such as myelin, interneurons expressing parvalbumin (PV), and peri-neuronal nets (PNN), mature late and are downregulated in persons with schizophrenia, leading to excitatory-inhibitory imbalance. Reduced expression of brain-derived neurotrophic factor (BDNF) affects neuron size, dendritic branching, and synaptic density early in the disease's progression and disrupted neuromodulatory systems including the dopaminergic and cholinergic systems alter the important function of plasticity gating. B. The outcome of dysregulated plasticity has profound effects on cognition as deficits apparent at very early stages of processing can be amplified at later stages. In this example, noisy sensory processing disrupts the perception of an auditory stimulus (1) along the auditory pathway. A reduced cortical signal-to-noise ratio in the auditory cortex (2) is then propagated to higher-order regions (3), a problem that is compounded by reduced inhibitory control from the frontal cortex in schizophrenia. Problems with higher-order processing can be expressed as deficits in attention, working memory, problem solving, and sensory learning. C. As many of the cognitive deficits seen in schizophrenia are attributed to disrupted plasticity mechanisms, remediation strategies have generally targeted these mechanisms. In particular, cognitive training programs have been proposed to improve higher-order functions in a non-invasive manner. However, individual differences in plasticity can determine a person's specific deficits as well as how they will respond to training. D. Pharmacological influences (both prescription and non-prescription drugs) can affect regulators of plasticity, cognition, and remediation. Most drugs developed to treat schizophrenia influence neuromodulatory systems; for instance, antipsychotics largely act on the dopaminergic system. Unfortunately, while these medications are helpful in controlling the positive symptoms of the disorder, they do little to alleviate the negative symptoms and can actually worsen cognitive symptoms. However, just as individuals can benefit from targeted cognitive training programs, personalized pharmacological treatment could be combined with remediation strategies to improve overall management of symptoms.

been reported in schizophrenia, primarily in the prefrontal cortex (Fung et al., 2010; Mellios et al., 2009). PV interneurons can facilitate information/sensory processing by controlling the output of pyramidal neurons. They also serve a critical function in the regulation of the critical period timing (Takesian and Hensch, 2013). Consequently, in schizophrenia, these PV+ interneurons may fail to regulate during adolescence the synaptic pruning of pyramidal cell circuits (Morishita et al., 2015). Furthermore, a recent study using a rodent model of schizophrenia demonstrated that fast-spiking interneurons in the auditory cortex—which are primarily PV interneurons—of mice carrying the 15q13.3 microdeletion exhibited deficient processing of auditory stimuli, resembling encephalography recordings in patients with schizophrenia (Thelin et al., 2017). Future studies should attempt to develop a mechanistic understanding of how a dysfunction of PV+ interneurons in schizophrenia can contribute to its symptoms and how we can leverage this knowledge to develop better treatment strategies.

Also contributing to plasticity inhibition and runaway pruning in schizophrenia are a group of specialized extracellular matrix structures, the PNNs (Berretta, 2012). Indeed, a growing body of evidence has highlighted the involvement of PNNs in schizophrenia (Mauney et al., 2013; Pantazopoulos et al., 2015; Pantazopoulos et al., 2010). PNN effects can be wide-ranging, and include synaptic dysregulation and altered firing properties of PNN-bearing neurons, (Pantazopoulos et al., 2006; Brückner et al., 1993).

Furthermore, PNNs do not reach maturity until late adolescence and early adulthood, a time course that overlaps with the typical prodromal period and the average onset of schizophrenia (Hensch, 2004; Penn, 2001; Sturman and Moghaddam, 2011). PNN changes observed in the visual cortex and other subcortical regions (Mauney et al., 2013; Pantazopoulos et al., 2010) suggest that populations in specific cortical areas are selectively impacted. However, this also implies that PNN alterations may not occur in sensory cortex such as auditory cortex, and requires further study to determine if PNNs play a role in the dysregulation of auditory cortical plasticity in schizophrenia.

BDNF, a subclass of neurotrophins that is secreted following neuronal excitation (Egan et al., 2003; Mowla et al., 1999), has been shown to modulate the release of dopamine and glutamate (Paredes et al., 2007), and thus can indirectly affect cortical plasticity through its effects on neuromodulator systems. Several lines of evidence have also suggested that BDNF may serve a critical role in the development of schizophrenia. For instance, reduced BDNF levels have been found in the blood (Green et al., 2011) and the brain of individuals with schizophrenia (Islam et al., 2017). Similarly, post-mortem studies have shown a significant reduction of BDNF transcripts (Reinhart et al., 2015; Thompson Ray, 2011) or protein expression (Hashimoto, 2005; Rao et al., 2015) in brain regions implicated in schizophrenia. Changes in BDNF protein levels (possibly resulting from mRNA expression changes) are also known to affect neuronal cell size, dendritic growth, and synaptic density (Causing et al., 1997; Katoh-Semba et al., 1997), which are all implicated in schizophrenia development. In addition, polymorphisms in the BDNF gene are believed to constitute a significant risk factor for schizophrenia in various populations (Li et al., 2013; Neves-Pereira et al., 2005). Furthermore, BDNF levels have been shown to significantly increase in patients undergoing cognitive training programs, which also correlated with improved quality of life measures (Vinogradov et al., 2009), highlighting the usefulness of BDNF as a potential biomarker for cognitive improvements in schizophrenia.

As highlighted above, neuromodulator systems can significantly affect brain plasticity, and dysfunctions in several such systems have been linked to schizophrenia. For instance, recent evidence points to nicotinic acetylcholine receptors (nAChRs) as underlying many of the pathophysiological features of schizophrenia (Hashimoto, 2005; Young and Geyer, 2013). In particular, the α7 nAChR subtype has been associated with the auditory P50 suppression in schizophrenia and suggests that auditory sensory gating could serve as an important translational biomarker (Hashimoto, 2015). For instance, α7 nAChR density has been shown to correlate with the inhibitory gating of the rodent P20-N40 auditory evoked potential (Stevens et al., 1996), generally considered the rodent equivalent of the human P50 (Adams and Stevens, 2007). In schizophrenia patients, clozapine has been reported to normalize P50 suppression (Nagamoto et al., 1999; Light et al., 2000; Olincy and Freedman, 2012). It is believed that the clozapine blockade of 5-hydroxytryptamine-3 (5-HT_3) receptors results in the release of acetylcholine from presynaptic terminals, which in turn stimulates α7 nAChR in the brain (Shirazi-Southall et al., 2002; Hashimoto, 2015). Similarly, nicotine has also been demonstrated to restore P50 anomalies in schizophrenia (Adler et al., 1993). Overall, these findings highlight that dysfunctions within the cholinergic system in schizophrenia can significantly affect cortical plasticity and sensory gating mechanisms within the auditory system. More work, however, is still needed to better link deficits in cortical plasticity with the wide range of auditory deficits that are observed in schizophrenia. Furthermore, it remains unclear whether the dysregulation of cortical plasticity precedes or develops after the onset of schizophrenia.

3. Treatments targeting plasticity regulators in schizophrenia

A complete summary of the various pharmacological agents that have been studied as potential treatments for schizophrenia is beyond the scope of this article. For a more comprehensive analysis of the agents and targets, we refer the reader to Lin et al. (2014), Miyamoto et al. (2012), and Köster et al. (2014). The following paragraphs will highlight some of the primary and most successful agents that have been investigated.

The dopamine model of schizophrenia is primarily based on the finding that chlorpromazine, an antipsychotic medication, significantly attenuates the symptoms of schizophrenia (Delay et al., 1952). This effect has since been linked to the successful blockade of D2-type dopamine receptors (Seeman and Lee, 1975). Although this discovery dates from several decades ago, most current antipsychotic medications prescribed for schizophrenia all still target dopamine (Miyamoto et al., 2012). Unfortunately, although these drugs help control the positive symptoms of this disorder, they only have a minimal effect on negative or cognitive symptoms. They do, however, provide indirect evidence suggesting dopaminergic involvement in the emergence of auditory hallucinations given that antipsychotic medications significantly reduce their occurrence.

In addition to the fact that most antipsychotic medications do little to alleviate negative or cognitive symptoms, some treatments can hamper a patient's ability to benefit from behavioral interventions intended to improve cognitive functioning. Indeed, schizophrenia is commonly treated with a range of medications that raise serum anticholinergic activity, which in turn affects nicotinic and muscarinic receptors (Terry et al., 2006; Chew et al., 2006). Not only have increased serum levels been found to adversely affect cognitive abilities such as learning and memory (Tracy et al., 2001; Minzenberg et al., 2004) they have also been shown to be negatively correlated with an individual's response to cognitive training (Vinogradov et al., 2009).

Given that treatment regimens are increasingly geared towards improving functional outcomes as opposed to managing specific symptoms, a growing body of research is looking into new pharmacological agents that are more effective for improving cognitive functioning. The glutamatergic system and the nicotinic-cholinergic system are two of the most promising targets for cognitive functioning. Unfortunately, attempts at targeting glutamate and NMDA glutamate receptors (NMDAR) have so far been mixed. For instance, a meta-analysis found that D-serine, *N*-acetylcysteine, and sarcosine—NMDAR modulators—successfully reduced negative and cognitive symptoms of schizophrenia when combined with non-clozapine antipsychotics, whereas symptoms were actually worsened when combined with clozapine (Singh and Singh, 2011), suggesting that how different medications are combined can have drastically opposite effects. A recent clinical trial targeting

NMDAR with glycine and D-cycloserine did not produce better results than the placebo (Buchanan et al., 2007). Although some negative findings have been reported (Buchanan et al., 2007), a recent meta-analysis concluded that D-serine is moderately effective for reducing symptoms of schizophrenia (Cho et al., 2016). D-serine might be particularly effective for normalizing auditory processing in schizophrenia. A pair of recent studies by Kantrowitz and collaborators showed that the administration of D-serine can reverse many auditory electrophysiological deficits—such as the reduced MMN—and restore auditory cortical plasticity in schizophrenia (Kantrowitz et al., 2016, 2018). These findings strongly suggest that NMDAR dysfunction is a key contributor to auditory cortical plasticity deficits and should perhaps be a prime target for treatments aiming to improve auditory function.

Given the key role played by α7 nAChR in the emergence of auditory P50 deficits and significant cognitive impairments, this receptor is an encouraging therapeutic target for schizophrenia, especially for the hard to treat cognitive disabilities (Hashimoto, 2015). The use of several different α7 nicotinic acetylcholine receptor agonists has been shown to improve several cognitive and learning measures (Martin et al., 2004; Keefe et al., 2015; Preskorn et al., 2014). However, a more recent multi-center study with a large sample size did not find cognitive improvements with TC-5619, α7 nicotinic acetylcholine receptor agonist, regardless of the dose tested (Walling et al., 2016). Similarly, acetylcholinesterase inhibitors—agents already used in the treatment of Alzheimer's disease—have shown beneficial effects in individuals with schizophrenia in some studies (Zhu et al., 2014), but not in others (Lindenmayer and Khan, 2011). Therefore, it seems that although glutamatergic and cholinergic drugs show promise for normalizing auditory processing deficits and cognition in schizophrenia, alone they are not sufficient to result in meaningful clinical improvements.

Finally, several groups have investigated the effectiveness of oxytocin in improving social cognition (Bradley and Woolley, 2017). Indeed, the oxytocin system, which plays an important role in social cognition and behaviors in humans and other animals (Meyer-Lindenberg et al., 2011), is an excellent candidate for improving social cognition. Initial evidence supporting a link between neurotransmitter and dysfunction in schizophrenia patients comes from investigating oxytocin receptors, where specific nucleotide polymorphisms were shown to correlate with poor social cognition abilities (Davis et al., 2014a). Early treatment investigations showed that the effectiveness of social training was significantly improved when immediately preceded by the administration of intranasal oxytocin (Davis et al., 2014b). A recent Bayesian meta-analysis of identified randomized controlled trials (RCTs) suggested a moderate but promising link between intranasal oxytocin and high-level social cognition improvements (Bürkner et al., 2017).

Neuromodulator systems can also be targeted with non-pharmacological approaches, such as cognitive training therapies that aim to harness physiological mechanisms of brain plasticity. This approach attempts to specifically target neural system abnormalities that are implicated in the pathophysiology of schizophrenia using specially designed training strategies (Vinogradov et al., 2012). Indeed, several studies have demonstrated that interventions that target plasticity via perceptual learning paradigms can offset the effects of impoverished sensory inputs (De Villers-Sidani et al., 2010; Mishra et al., 2014; Mishra et al., 2015). Moving forward, it will also be necessary to develop brain plasticity-based recovery strategies that combine pharmacological and non-pharmacological approaches (Guercio et al., 2019; Michalopoulou et al., 2013). This approach was pioneered by Neal Swerdlow (2012) who highlighted the synergistic value of pharmacologically-augmented cognitive therapies (PACTs). Several clinical trials using a PACT approach are currently in progress and should provide evidence supporting this approach to treat schizophrenia symptoms. Further support for this approach comes from a rich animal literature investigating the pairing of neuromodulation and behavioral training. For instance, we have recently shown that pairing the neuromodulation of the cholinergic system with auditory behavioral training in rodents led to profound plastic changes in the functional properties of auditory cortical neurons that correlated with improved perceptual measures (Voss et al., 2016).

Finally, individual differences should be taken into account when developing recovery strategies. Indeed, there is enormous interindividual variability in the effects of neuromodulating drugs (Voss et al., 2017). Similarly, important inter-individual variability exists in the functioning of endogenous plasticity modulators and their response to cognitive training interventions (Störmer et al., 2012; Schliebs and Arendt, 2011; Murthy et al., 2012; Biagianti et al., 2017). Therefore, properly accounting for age, sex, and pathological condition is essential to develop personalized treatments that support the functional recovery of patients by utilizing the brain's innate capacity to change.

4. The noisy brain model of schizophrenia

One of the strongest clues to auditory dysfunction in schizophrenia is the presence of auditory hallucinations, which are reported in up to 80% of patients (Andreasen and Flaum, 1991; Shergill et al., 1998). Various hypothetical models have attempted to explain the emergence of such hallucinations, such as source monitoring theory, which postulates that hallucinations are the result of misattributed internal sensory stimuli to external sources (Boksa, 2009; Frith and Done, 1988), and expectation-perception theory, which posits that deviant predictive coding and associated prediction errors are to blame for auditory hallucinations (Fletcher and Frith, 2009; Nazimek et al., 2012). Common to both theories is the hypothesis that a key source of the deficits observed in schizophrenia results from an increase in neural noise. Although poor filtering of noise has long been considered to be at the core of processing difficulties in schizophrenia (Thomas, 1973), it wasn't until recently that evidence arose suggesting that the increase in neural noise is due to randomly spiking neurons that reduce the cortical signal-to-noise ratio (Winterer et al., 2000; Winterer and Weinberger, 2004; Rolls et al., 2008). It is hypothesized that the dysplastic state of the schizophrenic cortex produces baseline cellular activity that is unrelated to either exogenous or endogenous signals, which creates the basis for deficits across the spectrum of disturbed capabilities and symptoms in the disease (White and Siegel, 2016). Indeed, it has been suggested that the brains of individuals with schizophrenia have difficulty resolving ambiguous sensory signals, struggle to sustain top-down processes (Merzenich et al., 2014) and display neuronal processes that are typically associated with noisy brain processing (Hinkley et al., 2011; Chen et al., 2014). Consistent with this hypothesis, an fMRI study of auditory hallucinations revealed that patients who hallucinate showed less auditory cortical activation to external acoustic stimuli than patients who did not (Ford et al., 2009). Increases in internal neural noise are believed to exert a limit on perceptual and cognitive capacities, not unlike what is observed with normal aging, where an increase in poor signal-to-noise resolution leads to greater impairments (Welford, 1981; Mireles and Charness, 2002). This increase in neural noise is believed to result from age-related cortical dysplastic processes (Cisneros-Franco et al., 2018; Mishra et al., 2014; De Villers-Sidani et al., 2010).

Noise can be either internal (endogenous) or external (exogenous). Although the schizophrenia model posits that disease-specific dysplastic processes result in increased neural (internal noise) noise, we propose that this, in fact, leads to a cycle whereby the noise maintains the cortex in a state of increased plasticity. There is good agreement that noisy sensory inputs, whether originating from exogenous or endogenous processes, can maintain cortical neurons in an immature state (Cynader and Mitchell, 1980; Mower, 1991; Fagiolini et al., 1994), which then results in impaired cortical function (Pienkowski and Eggermont, 2010; Zheng, 2012; Gourévitch et al., 2014). Noise-exposed animals exhibit profound functional and structural markers of plasticity in the primary auditory cortex (A1) including tonotopic reorganization, broadening of receptive fields, decreased intracortical

connectivity, BDNF expression, and reduced inhibitory tone (Zhou et al., 2011; Zheng, 2012; Kamal et al., 2013). These plastic changes are believed to result from a down-regulation of inhibitory processes that stem from a reduction in statistically meaningful sensory inputs (Kamal et al., 2013; De Villers-Sidani and Merzenich, 2011; Zhou et al., 2011; Thomas et al., 2018). Environmental auditory noise has also been shown to reduce the population of PV+ and GABA inhibitory interneurons (Kamal et al., 2013), further highlighting the role played by reduced inhibitory neurotransmission in response to increases in environmental noise.

Furthermore, the auditory hallucinations observed in schizophrenia are not unlike other instances of phantom percepts, in that they almost invariably result from aberrant cortical plasticity mechanisms. In the auditory domain, phantom percepts like tinnitus are typically accompanied by a maladaptive plastic reorganization of the tonotopic map (Eggermont, 2006). Similarly, an improvement in phantom perception is generally accompanied by a reversal of the map reorganization (Engineer et al., 2011). Although the tinnitus percept primarily involves the auditory cortex, auditory verbal hallucinations in schizophrenia likely involve a broader network of brain areas including frontal and parahippocampal areas (Ffytche and Wible, 2014). Indeed, it has previously been suggested that a form of deafferentation (e.g. social withdrawal) may trigger the onset of schizophrenia (Hoffman, 2007) by producing plastic reorganizational changes within the brain areas involved in social cognition, which result in hallucinations or delusions (Hoffman, 2008).

5. Conclusion

Schizophrenia is a complex and multifaceted mental health disorder. Although the phenotype is generally described as an array of positive and negative symptoms, a growing body of work has demonstrated that significant perceptual impairments, particularly in the auditory modality, also characterize it. These impairments possibly emerge as a result of abnormal cortical plasticity mechanisms and dysregulated neurotransmitter systems that are consistently linked with schizophrenia. Fortunately, both neuromodulators and cortical plasticity mechanisms can be manipulated, even in adulthood, suggesting that these impairments could be reversed in schizophrenia. An important first step, however, will be to develop a better understanding of how plasticity is affected and regulated in schizophrenia and to establish which plasticity mechanisms are associated with specific auditory and cognitive impairments. Given that both neuromodulator systems and cortical plasticity mechanisms display immense inter-individual variability, the personalization of care should be at the forefront of all treatment and remediation strategies. Such a personalized approach should also incorporate an assessment of perceptual deficits—which are not typically tested in the clinic—as it will improve our understanding of the disorder at the individual level and will help to personalize treatment.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors contributions

PV and EdV-S conceived the paper. PV wrote the first draft of the manuscript. MT conceived and designed the figures. All authors (PV, MT, GG, EdV-S) contributed to and have approved the final manuscript.

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