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Magnetic Resonance Spectroscopy Investigation of Conditioned Auditory Percepts

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Magnetic Resonance Spectroscopy Investigation of Conditioned Auditory Percepts

Timothy I. Michaels, Ph.D.

University of Connecticut, 2020

The neurobiology of hallucinations is complex, and despite over a century of research it has yet to be fully characterized. The observation that auditory hallucinations occur in healthy individuals may provide new avenues for understanding its neurobiology in psychopathology. Bayesian approaches to perception suggest that aberrant experiences can be conditioned, with stronger effects in those prone to hallucinations. Through a combination of functional magnetic resonance imaging and magnetic resonance spectroscopy, the present study investigated whether differences in the endorsement of conditioned hallucinations was associated with differences in anterior cingulate cortex (ACC) glutamate and GABA levels in a healthy, college-aged sample that differed in their propensity to endorse perceptual abnormalities. Hallucinators were more likely to endorse false percepts and were more confident in their responses during a Pavlovian conditioning task that paired an auditory stimulus with a visual stimulus. Conditioned hallucinations were positively correlated with self-report scores of hallucination-proneness in daily life. Hallucinators had a higher ratio of glutamate to creatine in the ACC compared to a control region, but there were no such differences in GABA/creatine ratios. Conservatively, these results suggest that the predictive coding account of hallucinations in healthy individuals overlaps with the underlying neurobiology of psychosis in disease states, and that such an approach may be especially useful for understanding psychosis risk across development.

Keywords: Auditory Hallucinations, Predictive Coding, Magnetic Resonance Spectroscopy, Perceptual Abnormalities, Functional Magnetic Resonance Imaging.

Magnetic Resonance Spectroscopy Investigation of Conditioned Auditory Percepts

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B.A., University of Chicago, 2006

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APPROVAL PAGE

Doctor of Philosophy Dissertation

Magnetic Resonance Spectroscopy Investigation of Conditioned Auditory Percepts

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Magnetic Resonance Spectroscopy Investigation of Conditioned Auditory Percepts

Despite over a century of research, the pathophysiology of psychosis has yet to be fully characterized. The neurobiology of psychosis is complex and likely involves genetic, molecular and structural abnormalities across diverse brain regions (Lakhan & Vieira, 2009). Clinically, psychosis is characterized by a heterogeneity of symptoms including hallucinations, the strong conviction of a sensory experience in the absence of a percept, and delusions, holding strong beliefs in the absence of supporting evidence (American Psychiatric Association, 2013).

Psychotic experiences can contribute to the pathology of serious mental illnesses, such as schizophrenia (SZ), which affects 1% of the world's population (World Health Organization, 2012). The global public health impact of this severe and chronic mental illness is significant; schizophrenia is among the top 10 causes of disability in developed countries (Chong et al., 2016). Given the heterogeneity of clinical presentation and numerous risk factors, SZ likely reflects a state of equifinality in which many different potential pathways can lead to similar pathology (Uhlhaas et al., 2017). In order to elucidate more specific mechanisms, it is important to isolate clinical characteristics that confer increased risk and identify their underlying neurobiological mechanisms, thereby linking physiological markers of disease risk with symptom phenomenology.

One promising approach for an improved understanding of psychosis in disease is through characterizing the spectrum of psychotic-like experiences in healthy individuals (Zammit et al., 2013). Although psychosis occurs within various psychiatric disorders, psychotic-like experiences also occur in healthy individuals across development (Schlosser et al., 2012; Unterrassner, Wyss, Wotruba, Haker, & Rössler, 2017). When psychosis is present in mental illness, it contributes to marked changes in behavior, high levels of distress, and significantly

impact daily functioning (Paolo Fusar-Poli, Borgwardt, et al., 2013). However, perceptual aberrations alone are not necessarily associated with ill mental health (Goulding & Odehn, 2009). As many as 3% of individuals report psychotic-like experiences regularly, and 7% of individuals report a lifetime prevalence of psychosis experiences (Linscott & van Os, 2013). As many as 13.2% of the general population endorses hearing voices (Beavan, Read & Cartwright, 2011). These experiences include perceptual abnormalities (PA), which involve perceiving stimuli without an actual percept, as well as hallucinations, in which the experience of PA is accompanied by a strong belief in the reality-basis of these percepts without supporting evidence (Tucker et al., 1969). Understanding the phenomenology of psychosis on a continuum has important implications for uncovering factors that contribute to increased risk of conversion to a psychotic disorder, and characterizing potential overlap in underlying neurobiology of low level perceptual abnormalities and hallucinations (Powers et al., 2019; Unterrassner, Wyss, Wotruba, Ajdacic-Gross, et al., 2017). Furthermore, this approach may suggest new avenues for prevention, early intervention, and treatment (Addington, Addington, Abidi, Raedler, & Remington, 2017).

Perceptual abnormalities can include experiences such as hearing one's name being called, seeing shadows in the shape of a person, experiencing the sensation of a cell phone vibrating in one's pocket or hearing song lyrics (Marshall et al., 2019). Adolescence through young adulthood marks the prototypical period of symptom onset (Tor et al., 2018). For these individuals at clinical high risk, approximately 25% - 35% will eventually convert to a psychotic illness (Addington et al., 2015; Cannon et al., 2008), with approximately one-third converting in the first year after onset, another third in the second year, and the final third more than two years after onset (Powers et al., 2019). Yet for some, these experiences continue into adulthood

without accompanying distress or functional impairment (Pinheiro, Schwartz, & Kotz, 2018; A. R. Powers & Corlett, 2018). For another subset of individuals, attenuated psychotic symptoms remit completely (Addington et al., 2019; Simon et al., 2013). Characterizing clinical and neurobiological characteristics that distinguish these groups at onset could greatly improve targeted early intervention efforts.

Auditory perceptual abnormalities may be especially important from a phenomenological perspective for understanding conversion risk given that auditory verbal hallucinations occur in 60-80% of all patients with schizophrenia (Shergill et al., 1998). Understanding the continuum of shared neurobiology of perceptual abnormalities and auditory hallucinations will help provide new understanding of risk factors for conversion, and may lead to improvements in early detection and prevention. Yet linking the spectrum of psychotic-like symptoms to neurobiology may require a computational and cognitive neuroscience perspective (Adams, Stephan, Brown, Frith, & Friston, 2013; Corlett, Frith, & Fletcher, 2009; Sterzer et al., 2018). Bayesian approaches to perceptual learning suggest that these experiences are not simply passive processes, but rather may be informed by previous conditioning (Corlett et al., 2009). Higher order beliefs in the reality basis of these experiences is one of the distinguishing characteristics between perceptual illusions versus hallucinations (Teufel et al., 2015). Under a predictive coding approach, hallucinations occur when top-down prior beliefs about perceptual experiences are maintained without conforming sensory input, resulting in the creation of a sensory input that conforms with prior beliefs (Powers, Mathys, & Corlett, 2017; Sterzer et al., 2018). New computational approaches (Mathys, 2017; Mathys et al., 2014) allow for behavioral and physiological data to be leveraged for modelling higher-order beliefs to confirm whether perceptual experiences are informed by differences in the weighting of prior expectations versus

sensory input. It also provides a powerful tool for linking the neurobiology of perception and cognition with systems-level approach to the phenomenology of psychosis across a continuum.

Neurobiology of Hallucinations and Perceptual Abnormalities

Initial evidence suggests that conversion risk may be reflected in both the overlapping neural basis of hallucinations and in the neurocognitive impairments that characterize psychosis. The neurobiology of hallucinations has increasingly shifted toward emphasizing the role of altered N-methyl-D-aspartate (NMDA) receptor functioning (Horga & Abi-Dargham, 2019; A R Powers, Gancsos, Finn, Morgan, & Corlett, 2015). Converging evidence from basic and clinical research indicate that NMDA receptor antagonists, such as Ketamine, can model both the phenomenology and neurobiology of hallucinations (Marsman et al., 2013; Powers et al., 2015). NMDA receptor antagonists induce auditory perceptual abnormalities in healthy individuals (Krystal et al., 1994) and increase the frequency and intensity of auditory hallucinations in patients with psychosis (Kantrowitz & Javitt, 2012). These effects are most likely achieved through the role of NMDA receptor antagonists in increasing the release of the neurotransmitter glutamate through the inhibition of GABAergic interneurons (de Jonge, Vinkers, Hulshoff Pol, & Marsman, 2017; Kittelberger, Hur, Sazegar, Keshavan, & Kocsis, 2012; Paoletti, Bellone, & Zhou, 2013) Specifically, NMDAR hypofunction increases activation of top-down frontal activity, including the anterior cingulate cortex (ACC), which results in the suppression of sensory signaling through primary sensory areas (Ranson et al., 2019). In animal models, both the acute and chronic administration of NMDA receptor antagonist reliably reproduce the neurobiological abnormalities observed in the pathology of psychosis (Cordon et al., 2015; Kittelberger et al., 2012; Kort et al., 2017; Michaels, Long, Stevenson, Chrobak, & Chen, 2018). This includes reduction in the number of GABAergic interneurons in hippocampal regions

(Cunningham et al., 2006), increases in anterior cingulate cortex glutamate levels (Stone et al., 2014) and decreased synaptic plasticity in the prefrontal cortex (Zhang, Behrens, & Lisman, 2008). Several studies (Kokkinou, Ashok, & Howes, 2018; Stone et al., 2010; White et al., 2018) have demonstrated that cortical NMDAR hypofunction results in other neurobiological abnormalities consistently reported in psychosis, including increased striatal dopamine release (Kokkinou et al., 2018; Stone et al., 2010). However, given the complex interaction of these two neurotransmitter symptoms, (McCutcheon, Krystal, & Howes, 2020) and mixed findings regarding their role across different clinical aspects of psychotic illness, more evidence is needed to further characterize the effects of NMDA hypofunction on subcortical dopamine in the etiology of hallucinations.

In vivo studies of glutamate and GABA levels in individuals with psychosis provide further evidence of the putative role of NMDA hypofunction in the neurobiology of hallucinations (Kegeles et al., 2012; Rowland et al., 2013). ¹H magnetic resonance spectroscopy (1H-MRS or MRS) is a neuroimaging technique that assesses the chemical composition of tissues in a noninvasive manner by using the magnetic resonance of hydrogen to determine the concentration of metabolites (Chiappelli, 2018; Cohen & Sweet, 2011; Faro, Mohamed, Law, & Ulmer, 2012). MRS allows for the in vivo measurement of various metabolites, including glutamate (Glu), GABA, glutamine, or the combination of glutamate and glutamine (Glx)(Dhamala et al., 2019). A meta-analysis of ¹H- MRS studies (Marsman et al., 2013) in patients with psychosis compared to healthy controls reported increased levels of glutamate in the medial prefrontal cortex. Individuals with first-episode psychosis appear to have increased level of glutamate in the anterior cingulate cortex compared to healthy controls, and glutamate levels in frontal regions are positively correlated with psychosis symptom severity (Kegeles et

al., 2012). Unmedicated patients with first-episode psychosis also demonstrate increased Glu levels in the ACC (Poels et al., 2014).

Findings from MRS studies investigating glutamate levels in those at clinical high risk (CHR) for psychosis are somewhat mixed. Several studies report no differences in the level of glutamate (Fusar-Poli et al., 2011; Stone et al., 2009) or Glx (Keshavan et al., 2009; Purdon, Valiakalayil, Hanstock, Seres, & Tibbo, 2008; Yoo et al., 2009) between CHR and health controls. One study reported increased levels of Gln (Stone et al., 2009) and another increased Glu/Gln ratio (Tibbo et al., 2004) in high-risk unmedicated individuals compared to controls. A large multi-year study of CHR individuals (Addington et al., 2007, 2012) that includes a MRS neuroimaging component is currently being completed at several sites across North America and will likely contribute significantly increased sample in order to provide additional power to detect between-group differences in glutamate levels.

Fewer studies have examined alterations in GABA in high-risk, first-episode, or chronic patients with psychosis. Increased GABA levels have been reported in chronic patients with psychosis (Choe et al., 1994) and after four-to-six months of antipsychotic medication treatment (Choe et al., 1996). MRS studies of individuals high in schizotypal traits demonstrated increased levels of glutamate and decreased GABA levels relative to health controls (Fervaha & Remington, 2013; Lin et al., 2012) but such differences may be task-dependent (Duncan, Enzi, Wiebking, & Northoff, 2011). Two studies (Rowland et al., 2013 and Rowland et al., 2015) report decreased GABA concentrations in chronic patients, another (Ongur et al.) reported increased GABA in the anterior cingulate of chronic patients.

Two recent meta-analyses (Egerton, Modinos, Ferrera, & McGuire, 2017; Kumar, Vajawat, & Rao, 2020) examined GABA levels in chronic patients with psychosis and in CHR

individuals. In patients with schizophrenia, GABA levels were lower in the anterior cingulate cortex compared to healthy controls, but there were no between-group differences in other frontal regions (Kumar et al., 2020). Yet when comparing CHR individuals to healthy controls, there were no between-group differences across all MRS studies (Egerton et al., 2017) nor in studies using other neuroimaging techniques including positron emission tomography (PET) and single photon emission computed tomography (SPECT). Two separate studies (Wang et al., 2016; Modinos et al., 2018) report no difference in GABA levels in those at ultra-high risk for psychosis (those with clinical risk factors and a family history of psychosis), while one study (Da Silva et al., 2019) reported higher GABA levels in those at clinical risk and another (de la Fuente-Sandoval et al., 2016) in those at ultra-high risk. These mixed results suggest the need for additional studies investigating the role of prefrontal GABA levels in the prodromal stages of psychosis.

There are several potential explanations for the above-noted discrepancies across MRS studies. There is some evidence that antipsychotic medications decrease glutamate levels (Schwerk, Alves, Pouwels, & van Amelsvoort, 2014), including in the ACC. Between-study differences in magnetic field strength may also contribute to mixed findings. There are many methodological differences across studies that could impact the ability to detect differences, including voxel size, voxel placement, and pulse sequence parameters. Few studies controlled for differences in white matter and CSF volume and none of the studies compared findings to a control region. Comparison across MRS studies examining differences in GABA levels is especially difficult given the need for using J-editing techniques that distinguish GABA from overlapping signals of other metabolites (Mikkelsen et al., 2017). When GABA MRS procedures are implemented in a standardized fashion, the reliability and consistency of measurement is

greatly increased (Mikkelsen et al., 2018). Although GABA concentrations are typically referenced to total creatine (TCr) levels, due to its relative stability, there is some evidence that phosphocreatine (PCr), which is a large component of the TCr signal, may be altered in disease states (Turner & Gant, 2014). Given these challenges associated with measuring glutamate levels in medicated individuals, the variability in GABA measurement across studies, and the unclear role of glutamate and GABA in clinical high-risk individuals, additional studies are needed to further elucidate these proposed neurobiological abnormalities across the spectrum of psychotic experiences.

Dimensional Approaches to Perceptual Abnormalities

The endorsement and nature of psychotic-like experiences can be assessed through a variety of approaches, including through self-report and structured clinical interview. In help-seeking populations, the Structured Interview for Prodromal States (SIPS) (Miller et al., 2003) is the gold standard for clinical research and can be especially helpful for monitoring conversion to psychosis (Cannon et al., 2008; Powers et al., 2019). It collects detailed information regarding psychotic experiences including an individual's level of conviction, distress, and changes in behavior in response to PA. Yet the SIPS is time-consuming to administer, is primarily focus on current symptoms, has not been normalized in healthy individuals, and was primarily designed for use in non-clinical samples (Miller et al., 2002). The Structured Clinical Interview for DSM-5 Disorders (SCID-5) (First, 2014), while also time-consuming to administer and requiring supervised training in administration, has been utilized for both clinical and research purposes and maps onto diagnostic criteria in order to rule out a current or past psychotic diagnosis (Shankman et al., 2018).

An individual's predisposition toward experiencing perceptual abnormalities can be reliably measured through self-report (Chan et al., 2019; Kim et al., 2010; Kline et al., 2016, 2012; Ratcliff, Farhall, & Shawyer, 2011). These measures have historically been developed using a dimensional approach to understanding psychotic symptoms on a continuum (E. R. Peters, Joseph, & Garety, 1995), in contrast to structured clinical interviews that are based on discrete risk states (e.g., the SIPS) or categorical diagnostic labels (e.g., the SCID-5). Several measures of perceptual abnormalities and psychotic-like experiences have been developed and tested for use in healthy individuals (Ratcliff et al., 2011). Yet there is considerable variability in the underlying constructs being measured across measures (Unterrassner, Wyss, Wotruba, Ajdacic-Gross, et al., 2017). The Launay-Slade Hallucination Scale Revised (LSHS-R) (Bentall & Slade, 1985; Launay & Slade, 1981) is a 12-item self-report measure of an individual's propensity to endorse hallucinations. It was designed for use in healthy individuals (Launay & Slade, 1981), has strong psychometric properties including test-retest reliability (Waters, Badcock, & Maybery, 2003), and has been normed in large undergraduate (Aleman, Nieuwenstein, Böcker, & De Haan, 2001) and adolescent (Løberg, Gjestad, Posserud, Kompus, & Lundervold, 2019) samples. Previous studies using the LSHS-R provide strong support for hallucinations existing on a continuum given the scale's reliability in measuring this construct consistently across healthy individuals (Kråkvik et al., 2015), patients with psychosis, and those with a history of hallucinations (Levitan, Ward, Catts, & Hemsley, 1996). The LSHS-R is a particularly useful tool for examining current perceptual abnormalities in healthy individuals given its utility in being able to reliably track these symptoms in those who convert to psychosis and in instances where the persistence of these experiences is not associated with mental illness.

Among adolescents and young adults who experience hallucinations, a portion will not covert to a psychotic disorder but may go on to develop a broader constellation of traits consistent with or similar to schizotypal personality disorder (STPD) (Rossi & Daneluzzo, 2002). STPD is a mental health condition characterized by unconventional beliefs, social difficulties, perceptual abnormalities, and paranoia (American Psychiatric Association, 2013). Although the prevalence of schizotypal traits is high in CHR individuals, this overlap alone does not influence the risk for conversion to psychosis (Zoghbi et al., 2019). While the diagnosis of STPD is associated with functional decline and subjective distress, its prevalence in clinical samples is low (APA, 2013), perhaps due to a lack of help-seeking behavior in this population (Barkus et al., 2010). Indeed, many individuals high in schizotypal traits maintain adequate functioning, and there may be a propensity toward this phenotype in certain professions such as psychics (Pinheiro et al., 2018; Powers, Kelley, & Corlett, 2017), mediums, and shamans (Powers & Corlett, 2018).

The Schizotypal Personality Questionnaire (SPQ) is a 75-item self-report questionnaire of schizotypal traits in the general population (Raine, 1991). The SPQ has strong psychometric properties (Callaway, Cohen, Matthews, & Dinzeo, 2014; Fonseca-Pedrero, Cohen, Ortuño-Sierra, de Ábeniz, & Muñiz, 2017), has been tested and normed extensively in undergraduate, young adult, and nonclinical samples (Rossi & Daneluzzo, 2002; Unterrassner, Wyss, Wotruba, Ajdacic-Gross, et al., 2017; Unterrassner, Wyss, Wotruba, Haker, et al., 2017), and is consistent with clinician ratings of schizotypal traits in healthy individuals without personality disorders (Chan et al., 2019). Unlike other self-report measures that are limited to PA, subscales of the SPQ also measure cognitive symptoms consistent with the prodrome of psychosis (Axelrod, Grilo, Sanislow, & McGlashan, 2001; Callaway et al., 2014; Compton, Goulding, Bakeman, &

McClure-Tone, 2009; Fonseca-Pedrero et al., 2017; Yaralian et al., 2000). The combined cognitive-perceptual factor of the SPQ can therefore provide a strong indication of traits related to the cognitive and perceptual abnormalities that are common across CHR, SZ, and STPD individuals.

While there are currently significant clinical and research efforts aimed at identifying factors that predict conversion to psychosis from prodromal states, few self-report measures of perceptual abnormalities have been examined with respect to their predictive validity. The Chapman Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978), is a 35-item self-report questionnaire that assesses psychotic-like experiences such as unusual perceptual abnormalities, bodily sensations, and dissociation. It has strong predictive abilities across time and cultures (Chan et al., 2015; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994), and maps onto other measures of schizotypal traits. As many as 10% or more of CHR individuals who convert to a psychotic disorder are diagnosed with an affective form of psychosis such as bipolar disorder with psychotic features or major depressive disorder with psychotic features (Paolo Fusar-Poli, Bechdolf, et al., 2013). Previous studies (Chapman et al., 2020) demonstrate that the Chapman scales may be especially useful for capturing the co-occurrence of mood and perceptual symptoms.

Cognitive models of auditory hallucinations propose that the persistence of these experiences is mediated by one's beliefs (Garety & Hemsley, 1987). Delusions are tenaciously-held false beliefs that can include strongly held convictions related to the experience of perceptual abnormalities. In line with the fully dimensional view of psychotic symptoms, and the role of beliefs and expectation in the formation of these experiences, the Peters et al. Delusions Inventory (PDI) is a 21-item self-report measure that assess an individual's distress,

preoccupation, and conviction associated with various delusional beliefs (Peters & Garety, 1996; Peters et al., 1995). The measure has strong psychometrics properties and has been used in large samples of healthy individuals (Peters, Joseph, & Garety, 1999), patients with psychosis (Peters, Day, McKenna, & Orbach, 1999), and undergraduate population (Fonseca-Pedrero, Paino, Santarén-Rosell, Lemos-Giráldez, & Muñiz, 2012).

Cognitive Impairment in the Prodrome of Psychosis

Cognitive deficits are a well characterized clinical feature of psychotic illness (Goldberg, David, & Gold, 2003; Green, 1996; Green, Kern, Braff, & Mintz, 2000). Recent efforts to identify and treat CHR individuals have focused on the neurocognitive profile of these individuals including variability in cognitive abilities and related functioning at the onset of symptoms, during the prodrome, and upon conversion to psychosis (Addington, Liu, et al., 2017). Changes in cognition may not only be related to risk for conversion, but may precede frank psychotic symptoms (Fusar-Poli et al., 2012) and therefore may be especially important for early detection and prevention efforts.

CHR individuals who convert to psychosis on average have a lower full-scale IQ and lower processing speed compared to those who not convert (Seidman et al., 2012). For a subset of individuals, the onset of reduced processing speed occurs prior to the onset of attenuated psychotic symptoms. Other studies (Addington, Liu, et al., 2017; Seidman et al., 2010) have demonstrated working memory deficits and difficulties with verbal memory as markedly impaired in CHR individuals and a strong predictor of eventual conversion. The Digit-Symbol Coding subtest (Coding) of the Weschler Abbreviated Scale of Intelligence (WAIS-IV) (Weschler, 2010) is a well-validated and commonly-used measure of processing speed that has been tested in patient populations, large adult populations, and undergraduate samples (Cornelis

et al., 2014). Poor performance on this neuropsychological measure is associated with worse functioning in psychotic illness, and predicts the later severity of symptoms (Fusar-Poli et al., 2012). The Letter-Number Sequencing task (LNS) is a measure of working memory abilities that has been validated across several large samples, is known to be impaired in psychosis (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1995), and is correlated with positive symptom severity (Haut, Kuwabara, Leach, & Arias, 2000; Hurford, Marder, Keefe, Reise, & Bilder, 2011; Murtagh et al., 2010). The strong reliability and validity of both measures, their use in clinical and non-clinical samples, their ease of administration, and their relation to psychosis symptom emergence and severity, indicate strong ability to detect neurocognitive differences that relate to underlying neurobiological vulnerability to psychosis.

Predictive Coding Account of Psychosis

Perceptual experiences are not merely passive “bottom-up” processes but rather are informed by higher-order learning (Rao & Ballard, 1999; Seymour, 2004). This is supported by evidence that individuals infer the cause of sensory information (von Helmholtz, 1867). For example, the sensation of being tickled can be cancelled when anticipated, either from someone else or oneself. In order to successfully navigate the world, perceptual experiences are learned and inform expectations about future sensory experiences. These models of the world are updated when novel perceptual information conflicts with previously learned expectations (Adams et al., 2013; Sterzer et al., 2018). The accuracy of these predictions must be robust enough to resist change yet flexible enough to adaptively incorporate new sensory information. This predictive coding account of perception relies on the mathematical approach of Bayesian inference (Corlett et al., 2009). A sensory prediction is represented as a probability (prior) and is combined with incoming sensory data (likelihood, also represented as a probability) to create a

posterior probability, which reflects the most likely outcome based on prior predictions and current sensory experience (Sterzer et al., 2018).

As a theory of brain function, predictive coding provides an account of hierarchical sensory learning in which low level sensory predictions contribute to higher-order beliefs or schemas about the perceptual world (Corlett et al., 2009; Horga, Schatz, Abi-Dargham, & Peterson, 2014). Prediction errors occur when incoming data violates prior predictions (i.e., the difference between the mean of the prior and the mean of likelihood probabilities). The reliability of priors vs. sensory data is based on their respective weighting (Mathys et al. 2011). The overweighting of priors or incoming sensory data can result in erroneous updating of internal working models of the world or the creation of percepts that conform with expectations. If previously learned associations and experiences are maintained in the absence of incoming sensory data (increase precision of a prior belief), a percept is created that conforms with previous expectations (i.e., hallucination). If sensory data are too easily incorporated into internal working models (increased precision of sensory data), individuals develop strongly held beliefs that resist change (i.e., delusions)(Anandakumar, Connaughton, Coltheart, & Langdon, 2017; Corlett et al., 2009; Corlett, Taylor, Wang, Fletcher, & Krystal, 2010) .

Preliminary evidence provides support for hallucinations relying on disruption in the weighting of prior beliefs. Yet it is unclear whether such weightings are disrupted at different hierarchical levels. enhanced top-down signaling and increased precision of priors. Individuals who hear voices demonstrate reduced bottom-up connectivity from Wernicke's to Broca's area (Friston, 2005) and hallucinators are more susceptible to sensory conditioning, which has been associated with an overweighting of prior beliefs (Powers, Mathys & Corlett, 2017). When auditory information is uncertain, hallucinators are biased toward responding in a manner that is

consistent with a stronger weighting of prior beliefs (Cassidy et al., 2018). This bias could also be induced through the administration of amphetamines, consistent with the well-established role of striatal dopamine in the etiology of psychosis. Yet other evidence suggests that auditory verbal hallucinations (AVH) rely on weak priors given evidence that individuals who experience AVH are inaccurate in predicting the sensory consequences of internal speech (Horga & Abi-Dargham, 2019; Kort et al., 2017).

Predictive coding provides a computational framework for linking the phenomenology of hallucinations with the neurobiology of psychosis. GABA and glutamatergic functioning appear critical to the E/I balance, but perhaps differentially across the hierarchy of the brain. Weak priors at lower levels (primary sensory regions) may lead to relying on high-level abstract or semantic prior beliefs. A decrease in the precision of priors may be related to glutamatergic hypofunction and its effects on striatal dopamine release (Teufel et al., 2015). Ketamine and other NMDA antagonists alters excitatory/inhibitory balance (Jardi & Deneve, 2013). This is supported by evidence that perceptual abnormalities can be conditioned; when trained to associate a light with a tone, individuals who experience hallucinations were more likely to endorse perceiving the tone when the light was presented alone than those who do not experience hallucinations (Powers, Mathys & Corlett, 2017).

Predictive coding is consistent with several adjacent theories of hallucinations. Although individuals with psychotic disorders were especially susceptible to this effect (Kot & Serper, 2002), individuals without a diagnosed psychotic illness but who experience PA also endorsed conditioned hallucinations during the task, suggesting a common mechanism between pathological and phenomenological hallucinations. Individuals who experience perceptual

aberrations attribute importance to events that others would not find salient, a process that can be viewed as a form of prediction error (Kapur, 2003).

Functional neuroimaging data of conditioned auditory percepts indicate that when making correct rejections, hallucinators were less likely to engage the anterior cingulate cortex (ACC) compared to non-hallucinators (Powers, Mathys & Corlett, 2017). The ACC has been consistently implicated in both the neural activity of auditory verbal hallucinations (Zmigrod, Garrison, Carr, & Simons, 2016) as well as stimulus detection prediction (den Ouden et al., 2009) and audiovisual associative learning (Laurienti et al., 2003). It is involved in cognitive control (Barch, 2017) and in source monitoring of censoring information (Yeung & Nieuwenhuis, 2009). Yet the neurobiological underpinning of these ACC activation differences is largely unknown.

Current Investigation

The present study investigated the neurobiology of conditioned hallucinations through the use of MRS to collect in-vivo measurements of glutamate and GABA neurotransmitter levels in healthy individuals that vary in their endorsement of perceptual abnormalities. When compared to individuals who do not experience PA (STP- or minus), individuals who endorse PA consistent with schizotypal personality traits (STP+ or plus), will 1) be more likely to endorse false percepts (conditioned hallucinations), 2) will be more confident in their belief about the conditioned hallucinations, 3) will demonstrate differences in fMRI activation patterns consistent with the neurobiology of hallucinations, and 4) will demonstrate increased glutamate concentrations (as measured by the ratio of total glutamate to total creatine) and decreased GABA concentrations (as measured by the ratio of total GABA to total creatine) in the ACC compared to glutamate and GABA concentrations in a control region (paracentral lobule).

Through applying a predictive coding account of conditioned hallucinations in a healthy undergraduate sample, the present investigation aimed to provide further support for the top-down role of perception in psychotic experiences along a continuum, as well determine whether the neurobiological and cognitive mechanisms underlying perceptual aberrations overlap with the putative role of NMDA receptor hypofunction in psychosis.

Methods

All study materials, participant recruitment and protocol procedures were approved by the Institutional Review Board (IRB) of the Human Research Protection Program (HRPP) at the University of Connecticut. All participants had the opportunity to read and discuss the consent form and all participants provided informed consent before participating. Two groups of participants were recruited: 1) individuals without a diagnosable psychiatric disorder who endorse schizotypal traits (STP Plus/STP+) and 2) healthy individuals without a diagnosable psychiatric disorder who do not endorse schizotypal personality traits (STP Minus/STP-). Study recruitment occurred in two parts; during the first part (Phase A), participants were invited to participate in an online survey through the Department of Psychological Sciences participant pool. Those survey participants who met study criteria from Phase A were invited to the second part of the study (Phase B) which included an in-person screening visit. If eligible following the in-person screening visit, participants were enrolled in the neuroimaging portion of the study. In addition to recruitment through the Participant Pool, Phase B participants were also recruited through online and local advertisements in Storrs, Connecticut and Hartford, Connecticut. For Phase B, exclusion criteria were as follows for all participants: 1) current diagnosis of an Axis I psychiatric disorder (including psychotic disorders); 2) MRI contraindications and claustrophobia; 3) subject-reported substance dependence or active use; 4) pregnancy or possibility of pregnancy by self-report; 5) any medical or developmental problem that is known

to impair cognition significantly such as intellectual disability, attention deficit hyper activity disorder, Huntington's disease, Down Syndrome, or traumatic brain injury; 6) individuals with significant hearing impairment including those requiring the use of a sign-language translator; and 7) individuals with significant vision impairment such that they are unable to read the third line of a standard eye chart (with corrected vision).

Participants (Phase A)

The overall sample was comprised of 552 individuals, 98% of whom (542) were undergraduate students enrolled in introductory psychology courses at the University of Connecticut. Exclusion criteria for Phase A participants were as follows: 1) Self-reported first-degree relative with history of a diagnosed psychotic disorder (e.g., schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or bipolar disorder with psychotic features), 2) MRI contraindications and claustrophobia; 3) non-native English speakers and 4) incomplete survey response data. Based on the above-mentioned criteria, 173 participants (31%) provided incomplete data and were excluded from further enrollment. Of the remaining sample (n=379), a total of 137 survey participants (36%) were excluded based on the following: first degree relative with psychiatric diagnosis (n=105, 27%), non-native English speaker (n=21, 5%), MRI incompatibility (n=11, 2%). The remainder of the sample (n=242, 43%) were deemed eligible to continue and were invited via email to participate in Phase B of the study. Among those participants eligible from Phase A, participants with a LSHS total score above 20 (n=51, 21%) were classified into the STP+ group while those with LSHS total scores below 20 (n=191, 78% were classified into the STP- group. The LSHS total score of 20 was selected based on previous research demonstrating this score as approximating the median split in college student samples (Aleman et al., 2001; Waters et al., 2003).

Survey Measures (Phase A)

Participants in Phase A of the study completed several self-report measures including those that were utilized to determine their eligibility for Phase B. This included demographic information (e.g., sex, ethnicity, gender, age, and years of education), family history of psychosis diagnosis, language abilities, contraindications for MRI, and questions related to hearing or visual difficulties. Perceptual abnormalities were assessed using several different self-report measures. The Chapman Perceptual Abnormality Scale (Chapman et al., 1978) consists of 35 items that assess experiences such as bodily discontinuities and unusual sensory experiences. It has been validated in a large population of undergraduate students for the assessment of psychotic experiences (Chapman et al., 1994). The Peters Delusion Inventory (PDI) is a 21-item scale measure (Peters & Garety, 1996) of delusional beliefs that includes subscales of distress, preoccupation and conviction. It has been validated in an undergraduate sample (Fonseca-Pedrero et al., 2012). The Schizotypal Personality Questionnaire (SPQ) is a 75 item self-report questionnaire modeled on DSM-IV TR criteria for Schizotypal Personality Disorder (SPD) that contains subscales for all nine schizotypal traits (Callaway et al., 2014). The measure has been used extensively in assessing the screening for SPD in both clinical (Chan et al., 2019; Raine, 1991) and healthy individuals (Unterrassner, Wyss, Wotruba, Haker, et al., 2017). The Launay-Slade Hallucinations Scale (LSHS-R) is a 12-item measure frequently used to detect predisposition to hallucinations in normal individuals (Launay & Slade, 1981). It assesses three factors include vivid mental events, hallucinations with a religious theme, and auditory and visual hallucinations experiences (Aleman et al., 2001; Waters et al., 2003).

Participants (Phase B)

All participants that met inclusion criteria based on Phase A survey data were invited to participate in Phase B of the study. Twenty-three individuals completed in-person screening during Phase B, 12 individuals in the STP- group and 11 individuals in the STP+ group. Ten participants (66%) from the STP- group screened-in, and six of the 11 (54%) STP+ participants met inclusion criteria. Two of the eight (25%) STP+ participants that screened-in were lost to follow-up when scheduling the fMRI portion of the study; all of the eligible STP- participants continued to the second part of the study (Figure 1). Within the STP- group, one individual (16%) did not complete the fMRI due to a software error. MRS data for the control region were not collected in two of the nine (22%) participants from the STP- group due to time limitations and poor fit quality (Figure 1). In total, 15 participants completed Phase B procedures, 13 of whom (86%) completed all study procedures and provided both task and MRS data for analysis.

Clinical and Neuropsychological Assessments (Phase B)

During the first visit of Phase B, participants were screened through administration of the Structured Clinical Interview for the Diagnosis of DSM-IV-R disorders (SCID-IV) (First et al., 2002) to exclude any individuals that meet criteria for a current psychiatric disorder. Six of the 23 participants (26%) enrolled in Phase B (three participants in each group) were excluded due to currently meeting criteria for the following psychological disorders: Attention-Deficit/Hyperactivity Disorder (n=1), Bipolar Disorder (n=1), Generalized Anxiety Disorder (n=2), and Major Depressive Disorder (n=2). The remaining individuals (n= 15) were enrolled in the final phase of the study (Phase B).

To estimate participants' overall cognitive abilities, participants were administered the two-subtest form (Vocabulary and Matrix Reasoning subtests) of the Weschler Abbreviated Scale of Intelligence, Second Edition (WASI-II). The two-test version of the WASI-II provides a

brief, reliable measure of verbal and perceptual reasoning abilities in order to estimate overall cognitive abilities (Weschler, 2013). The WASI-II has strong psychometric properties (Dumont & Willis, 2008) and has been used in both clinical and research settings (Holdnack, Schoenberg, Lange, & Iverson, 2013; McCrimmon & Smith, 2013). Participants also completed additional neuropsychological measures including Letter Number Sequencing (LNS) and Digit Symbol Substitution Test (DSST). LNS is a measure of numeric working memory and demonstrates superior psychometric properties (Murtagh et al., 2010). It has been specifically investigated in patients with psychotic illness (Hurford et al., 2011) and correlates strongly with the severity of positive symptoms (Addington, Liu, et al., 2017; Haut et al., 2000). DSST is a timed measure of oral and visual processing speed that has been validated in a large normative sample and has strong psychometric properties (Lezak, Howieson, & Loring, 2004). Both patients with psychosis (Cornelis et al., 2014) and those with attenuated psychotic symptoms (Paolo Fusar-Poli et al., 2012) show reduced processing speed performance on the DSST.

fMRI Task and Behavioral Data

All stimuli were presented and responses were recorded through MATLAB Psychtoolbox 3.0 (Hernández Lorca, 2018; Kleiner et al., 2007). A white fixation cross was presented on a black background throughout each run. The visual stimuli consisted of a 4 x 7 square gray and black checkerboard pattern. Gray squares were presented at 25% brightness to maximize visual stimulation. The target auditory stimuli consisted of a 1-kHz tone with a 100-ms ramped envelope presented with a broadband white noise (130dB PSL). Scanner noise was estimated by sound-level meter to be at 130dB SPL. Participants were provided with in-ear headphones with foam earplugs for protection from scanner noise. The attenuation afforded by the headphones was deemed to be 40dB SPL and therefore target stimuli were adjusted to be presented at 90 dB

PSL to account for the attenuation. During the task, target tones were presented at 0% (no tone), 25%, 50% and 75% likelihood of detection as determined by the QUEST thresholding paradigm.

Participants who screened-in Phase B Part 2 practiced the condition hallucination task outside the scanner on a 2017 Apple MacBook Pro laptop with a pair of AKG (Vienna, Austria) K240 Professional Studio headphones prior to completing the task in the scanner. The task was run in Matlab Version 2018b through the PsychToolbox 3.0. Task instructions were provided verbally and participants were tested on their understanding of task instruction during the practice run. The practice session used the same stimuli, task components, and scanner noise as the fMRI component. During the practice component, participants responded whether the auditory stimuli was present as well as their confidence in their response and were required to achieve over 85% accuracy to continue in the study.

During the fMRI portion of the study, participants completed stimulus thresholding prior to test runs using the QUEST maximum-likelihood-based procedure (Watson & Pelli, 1983). Threshold testing determined the stimulus intensity threshold for 75% likelihood of detection of target stimulus embedded in noise for each participant. Individual psychometric curves were fitted given participants responses, and stimulus intensity of 25% and 50% detection were derived based on these psychometric curves. During the main test trials of the experiment, target tones were presented at levels estimated to correspond to these (75%, 50%, and 25%) likelihoods of detection. Total trial length during the thresholding procedures was 2500ms. Training trials establish a relationship between a conditioned stimulus (a clearly-presented 4x7-square checkerboard pattern, gray on black, presented at 25% brightness), and the unconditioned stimulus (a 1-kHz tone with 100-ms ramped envelope with broadband white noise presented at 130dB SPBL). Training trials consists of the presentation of a fixation (500-1000ms form trial

start) followed by presentation of the visual stimulus concurrent with the auditory stimulus for one second.

Test trials consisted of 12 blocks of 30 trials over 3 blocks per functional run. Unlike training trials, test trials included target-absent trials (0% threshold) in which the unconditioned stimulus was not presented. Trial-type relative likelihoods were determined by block number and trial type presentation was pseudorandomized within block. During the QUEST procedure, participants reported whether the tone was present or not present. During training and test trials, participants reported whether the tone was present and how confident they were in their answer on a scale from 0 (not confident) to 5 (very confident) over a 2000-ms response period (Figure 2). Positive responses in the absence of the unconditioned stimulus were considered a hallucinated percept. When responses were not recorded in time, the stimulus intensity corresponding to that trial was repeated during the next trial.

MRS Data Collection

All MRI procedures were conducted on a Siemens Prisma 3 Tesla scanner (Berlin, Germany) with a 64-channel head coil at the University of Connecticut Brain Imaging Research Center (Storrs, CT). ECG and respiration recordings were conducted using an MRI-compatible equipment. Participants were provided with in-ear noise-cancelling headphones that ran through a Silent Scan audio system (Avotec, Stuart, FL) and were provided a 1x2 response box (Current Designs, Inc., Philadelphia, PA) in their right hand for the task. The task was presented through the Psychtoolbox application in MATLAB Version R2018a (MathWorks, 2018) running on a PC and projected onto a 24" BOLDscreen LCD display viewed through a double mirror fitted to the head coil (Cambridge Research Systems, Kent, UK). Prior to running participants, in-scanner noise was measured and used to calibrate the decibel output of task audio stimuli.

Participants completed Localizer, Field Map A/P and Field Map P/A scan sequences prior to fMRI and MRS scans. Three-dimensional high-resolution anatomical scans were acquired using a magnetized prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (Echo time [TE] = 2.98ms, Repetition time [TR] = 2300ms, Flip angle [FA] = 9°, number of excitations [NEX] = 2) that produced 176 T1-weighted images with a field of view (FOV) of 26cm and voxel sizes of 1.0 x 1.0 x 1.0mm. Participants were instructed to keep their head still and watched a movie of their choice during these initial scans. During the task, a multiband (factor=3) pulse sequence was run (Echo time [TE] = 30.20ms, Repetition time [TR] = 1070ms, Flip angle [FA] = 57°, number of excitations [NEX] = 2) that produced 60 slices with a field of view (FOV) of 210mm and voxel sizes of 2.5 x 2.5 x 2.5mm. The thresholding procedure was five minutes long while training and test trials lasted approximately 40 minutes (four nine-minute runs).

For the MRS portion of the task, voxel templates were created through the Voxel Positioning System (Hancock, 2019) pipeline in ParaView (Kitware, Clifton Park, NY), an open-source, multi-platform data visualization application. The dimensions for the MRS volumes of interest (VOI) were as follows: (1) anterior cingulate cortex (ACC): size 24 x 24 x 21 mm, and (2) paracentral lobule (PCL): size 20 x 20 x 20mm. The median sagittal plane was selected as a reference slice for voxel positioning. All of the VOIs were positioned in such a manner as to avoid the ventricles and skull and minimize the percent white matter and CSF in the VOI. Manual adjustments were applied for each participant to ensure that the Full Width Half Max (FWHM) of the spectral peak was below 25 Hz. A Point Resolved Spectroscopy Sequence (PRESS) sequence (Yahya, Mädler, & Fallone, 2008) was used for glutamate detection (Mullins, 2008) with the following parameters: TR = 2000 ms; TE = 40 ms; 128 signal averages;

acquisition bandwidth = 2000 Hz. A symmetric-suppression (Mullins et al., 2014) Mescher-Garwood Point Resolved Spectroscopy Sequence (MEGA-PRESS) (Baeshen et al., 2019; Dhamala et al., 2019; Mullins et al., 2014) was used for GABA detection with the following parameters: TR = 2000 ms; TE = 80 ms; 64 signal averages; acquisition bandwidth = 2000 Hz. During odd-numbered acquisitions, a frequency-selective, Gaussian inversion pulse was applied to GABA-³CH₂ resonance at 1.9 ppm, affecting the weakly J-coupled triplet peak of GABA-⁴CH₂ at 3.01 ppm (EDIT-ON). During even-numbered acquisitions, the same pulse was applied at 1.5 ppm, symmetrically to the 1.7 ppm coupled macromolecule spins (EDIT-OFF). The GABA-edited spectrum was obtained from the difference between the EDIT-ON and EDIT-OFF spectra. For quantification, a shorter measurement (16 averages) of the unsuppressed water signal from the same volume was obtained. Variable power optimized relaxation delays (VAPOR) (Tkacik et al., 1999) were applied for water suppression. Shimming was performed automatically before each acquisition. Three consecutive MEGA-PRESS scans were acquired for each participant for each region.

Survey and Behavioral Data Analysis

Survey data were collected and exported from Qualtrics through the University of Connecticut's Psychological Experiment Pool. All survey data was analyzed in R Studio (RStudio Team, 2015). Chi-square and unpaired two-sample t-tests were run to examine group differences in demographic variables and self-reported levels of psychotic-like symptoms, and auditory stimuli detection threshold. Behavioral data from the fMRI task was analyzed using custom Matlab scripts provided by Powers and colleagues (2017). An unpaired two-sample t-test examined between-group differences in detection threshold (db SNR), in the probability of participants responding "yes" at each detection likelihood (no stimuli present, 25%, 50%, and

75%). An analysis of variance (ANOVA) was run to determine whether there was a significant between-group difference in participants' confidence when responding 'yes' or 'no' at each detection likelihood during test trials.

fMRI Data Analysis

Preprocessing and functional analysis was conducted using AFNI (Cox, 1996) and FSL (FMRIB Software Library). Functional runs from each subject were corrected for slice acquisition time, realigned to the middle volume of the series, spatially smoothed with a Gaussian kernel (6 mm FWHM) and the time series was high-pass filtered using Gaussian-weighted least-squares (max= 1/128 Hz). Functional data were linearly aligned to Montreal Neurological Institute (MNI) space. All four task runs were combined into a single run, the first 6 TRs were removed from both imaging data and stimulus timing files. Single subject data were analyzed using a fixed effects model with task modeled as a canonical hemodynamic response. For the purpose of analysis, trials were split by response type ("yes" or "no") and stimulus intensity (likelihood detection). Contrasts included each response type and detection likelihood ("0Yes," "0No," "25Yes," "25No," "50Yes," "50No", "75Yes", and "75No"), and difference in responding yes versus no to no-tone ("0Yes" – "0No"). For whole brain analysis, statistical maps used a threshold of $p < .01$ and one-sided (NN=3) cluster significance of $p < .05$. The lowest FDR q-value was 0.9. A region-of-interest (ROI) analysis was conducted for bilateral anterior cingulate cortex (ACC) and paracentral lobule (PCL) (four regions total). An ROI mask was created by resampling the statistical dataset to ensure same resolution and boundaries across subjects and group. Beta weights were extracted for each region and each contrast.

MRS Data Analysis

MRS data were analyzed using the FID-A (Simpson, Devenyi, Jezzard, Hennessy, & Near, 2017) toolkit in MATLAB, custom python scripts, FSL (Oxford University, Oxford, UK), and Tarquin (Wilson, Reynolds, Kauppinen, Arvanitis, & Peet, 2011) to fit the spectra. Custom python scripts were used to parse the MRS DICOM files, create a VOI mask for each region, and merge each of the runs (three runs each for PRESS and MEGA-PRESS sequences). Using the FID-A toolkit, all spectra were phase aligned with reference to water, bad averages were removed, corrected for frequency drift and phase drift, zero filled from 1024 to 4096, apodized with a 4 Hz Gaussian filter, and frequency aligned. Initially, spectra were frequency aligned to N-acetylaspartate (NAA) at 2.02 ppm, however due to the instability of NAA as a reference, spectra were separately aligned to creatine (Cr) at 3.02 ppm. Normalizing to creatine reduces intersubject variance attributable to differences in global signal strength and has been shown to yield reliable GABA concentration estimates (Bogner et al., 2009). Peak integration was used to quantify total concentrations of each metabolite. The final spectra were visually examined for artifact and quality of the fit. For each subject, FSL was used to segment tissue volume in order to derive CSF and white matter volumes which were applied to each VOI and used as control variables in all statistical analyses.

The ratio of total Glu/total creatine and GABA/total creatine was used for hypothesis testing. Statistical testing was also conducted using NAA as the denominator in the ratio. For each statistical test, were entered as control variables. All statistical analysis of group differences in VOI glutamate and GABA concentrations was conducted in R Studio.

Results

Characteristics of Study Subjects

There was no significant between-group difference in age ($t(13) = 0.26, p = 0.80$), gender ($\chi^2(1, N=16) = 0.00, p = 1.00$), ethnicity, ($\chi^2(1, N=16) = 3.89, p = 0.14$), sexual orientation ($\chi^2(1, N=16) = 0.07, p = 0.79$), or number of years of education ($t(14) = 0.24, p = 0.82$) (Table 1). There was also no between-group difference in full-scale IQ (FSIQ) ($t(13) = 1.40, p = 0.19$). These demographic variables also did not differ significantly between group when only including those participants that completed all procedures.

Participants completed several self-report measures that assessed their propensity to experience perceptual abnormalities and delusional beliefs. There was a significant between-group difference in total scores on the Launay-Slade Hallucination Scale, ($t(14) = -5.42, p < 0.001$), which has previously been shown specificity for experiencing auditory hallucinations (Aleman et al., 2001; Levitan et al., 1996; Waters et al., 2003). There were no between-group differences on other measures of psychotic-like experiences including perceptual aberrations (Chapman Total Score, $t(14) = -0.28, p = 0.78$), schizotypal traits (SPQ Total Score, $t(14) = -1.37, p = 0.19$), and delusional beliefs (PDI Total Score, $t(14) = -1.59, p = 0.14$) (Table 2). There were also no significant between-group differences on subscales of the SPQ that have previously been associated with perceptual abnormalities and schizotypal traits such as the cognitive/perpetual subscale ($t(14) = -0.95, p = 0.36$), and perceptual abnormalities subscale ($t(14) = -1.78, p = 0.10$). Across several different measures of schizotypal traits and susceptibility to experience perceptual aberrations, the only significant group difference emerged in total LSHS-R scores.

In addition to IQ testing, participants that screened into Phase B of the study completed tests of working memory and processing speed that have been previously demonstrated to differ between healthy individual and those with psychosis (Cornelis et al., 2014; Murtagh et al., 2010) as well as those at-risk for psychosis (Addington, Liu, et al., 2017; Paolo Fusar-Poli et al., 2012). There was also no between-group difference in processing speed as measured by differences in the average T-score on the Digit Symbol Substitution Test (DSST), ($t(14) = 1.35, p = 0.20$). There was also significant between-group difference in working memory abilities as measured by group differences in average T-score on the Letter Number Sequencing test (LNS), ($t(14) = 1.51, p = 0.15$).

Task Performance

There was no significant difference in the detection threshold between groups ($t(12) = 1.41, p = 0.18$), indicating that differences in task performance were not likely driven by individual or group differences in the decibel level of the target audio stimuli (Figure 3A). Participants in the STP+ group were significantly more likely to response “yes” during the no-tone condition ($t(12) = -2.30, p < .05$), however there was no significant differences in the probability of endorsing a response at the 25% ($t(12) = -1.03, p = 0.32$), 50% ($t(12) = -0.04, p = 0.92$), or 75% ($t(12) = -0.06, p = 0.94$) detection threshold (Figure 3B). Across all participants, the probability of responding “yes” when there was no tone positively correlated with self-reported hallucination severity as measured by LSHS-R total scores ($R^2 = 0.31, p < .001$) (Figure 3C). Overall these results are consistent with previous findings that voice-hearers without a psychosis diagnosis are more likely to endorse conditioned hallucinations (A R Powers et al., 2017), and this effect is not accounted for by group differences in auditory detection thresholding. It is also consistent with previous findings of a strong positive linear relation

between hallucination severity, as measured by LSHS-R total score, and the probability of endorsing conditioned hallucinations.

In addition to responding whether or not the tone was detected, participants rated their level of confidence in their answer during each test trial. Participants rated their confidence similarly across most conditions. There was no group-by-condition difference in confidence ratings at the 25% ($F(3, 22) = 0.68, p = 0.58$), 50% ($F(3, 22) = 0.11, p = 0.96$), or 75% ($F(3, 22) = 3.36, p = 0.07$) detection threshold (Figure 3C). However, there was a significant between-group difference in confidence ratings in the no-tone (0% detection) condition ($F(3, 22) = 3.93, p = .05$), which was driven by a higher confidence in “yes” responses to the no-tone condition in the STP+ group compared to the STP- group ($t(14) = -3.36, p < .01$). This provides further support for the higher likelihood of endorsing false percepts in the STP+ group being driven by a strong belief in the association of the conditioned stimuli, rather than less confidence in their predictions. Yet there was no significant correlation between hallucination severity and the confidence with which conditioned hallucination were reported ($R^2 = 0.08, p = 0.32$). It is likely that the high variability in confidence ratings in the STP+ group, and low samples size, decreased the ability to detect and association between confidence ratings and hallucination severity.

fMRI Results

Whole-brain fMRI analysis revealed few clusters that survived statistical correction. Cluster-based correction revealed small regions of activation across several contrasts ($k < 20$). When responding “yes” to no-tone trials (endorsing conditioned hallucinations), the STP+ group demonstrated higher activation than the STP- group in several regions previously associated with the neurobiology of hallucinations (Figure 4) including the cerebellum ($k = 6, Z = 3.12$, peak at

20, 31, -45), right middle frontal gyrus ($k=4$, $Z=3.19$, peak at 25, -52, 3), superior temporal gyrus ($k=3$, $Z=3.13$, peak at -43, 6, -15), thalamus ($k=3$, $Z=3.12$, peak at 20, 31, -45), right insula ($k=3$, $Z=3.12$, peak at 20, 31, -45), and right middle cingulate cortex ($k=3$, $Z=3.12$, peak at 20, 31, -45). However, there were also clusters in regions that have not been associated with auditory verbal hallucinations including the brain stem ($k=5$, $Z=3.56$, peak at 8, 26, -30) and right cerebellum white matter ($k=3$, $Z=3.29$, peak at 28, 46, -47). Although these results provide some evidence that conditioned hallucinations activate the same regions consistent with previous studies (Zmigrod et al., 2016) on the neurobiology of hallucinations in psychotic disorders, and that activation patterns appear to differ between groups, these results should be interpreted cautiously given the sample size, number and size of clusters that survived statistical correction, and relatively large q value (0.5).

When subtracting “no” responses from “yes” responses during no-tone trials, the STP+ group demonstrated higher levels of activation in several regions hypothesized to be involved in the neurobiology associated with the overweighting of top down priors including the left inferior frontal gyrus ($k=18$, $Z=3.21$, peak at -53, -35, -5), left middle temporal gyrus ($k=15$, $Z=3.28$, peak at -55, 26, -2) and right caudate ($k=6$, $Z=3.18$, peak at 13, -22, -11). The majority of the clusters that reached statistical significance were also notably small in size (Figure 4B). While providing some consistent evidence of overlap in the neurobiology of conditioned hallucinators with hallucinations in psychotic disorders, these results should be interpreted conservatively given the above-noted limitations of the sample size, cluster-based correction, and whole-brain exploratory fMRI analysis approach.

Given this study’s a prior hypothesis on the role of ACC glutamate and GABA dysfunction in the neurobiology of conditioned hallucinations, a region-of-interest (ROI) fMRI

analysis was conducted for the bilateral ACC and control region (PCL). During conditioned hallucinations, hallucinators exhibited higher levels of activation in several voxels with the right ACC ($B = 0.57$, $q = 0.05$, $p = 0.001$) but not the left ACC (Figure 5A). There were also significant between-group activation differences within the right PCL ($B = 0.47$, $q = 0.05$, $p = 0.001$), contrary to stated hypotheses (Figure 5B). Similar unilateral patterns of activation differences emerged in the right ACC ($B = 0.45$, $q = 0.05$, $p = 0.003$) (Figure 5C) and right PCL ($B = 0.18$, $q = 0.05$, $p = 0.003$) (Figure 5D) when subtracting “no” responses from “yes” responses to no-tone trials. The magnitude of these activation differences was notably smaller compared to the conditioned hallucinations contrast. There were no between-group differences in the left ACC or left PCL for either contrast. ROI analysis of the ACC during correct rejections (“no” responses to no-tone trials) demonstrated lower levels of activation in the STP+ group compared to the STP- group (not shown), consistent with previous findings (Powers et al., 2017). Given increases in activation of frontal regions during conditioned hallucinations, consistent with the hypothesis of overweighting top-down priors, this finding suggests that hallucinators exert less cognitive control during correct rejections, perhaps due to difficulties with stimulus detection (Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005).

MRS Results

A multiple linear regression model was used to examine between group differences in the ratio of Glu/Cr and GABA/Cr in the ACC compared to the control region, and to examine between-group differences in cortical excitability (Glu/GABA ratio). For all linear models, individual differences in the percent of cerebral spinal fluid and percent of white matter were entered as control variables. While there was no significant group x region interaction in the ratio of glutamate to creatine, $F(2,25) = 1.83$, $p = 0.18$, there was a significant between-group difference in glutamate concentration in the anterior cingulate cortex, $F(1,13) = 4.57$, $p = 0.05$,

but no such difference in the control region, $F(1,11) = 0.77, p = 0.40$, (Figure 6A). The finding of higher levels of ACC Glu/Cr ratio is consistent with predictions and previous MRS studies of individuals with psychosis (Marsman et al., 2013). The inability to detect a group x region interaction may have been driven by low variability in PCL Glu/Cr concentrations in the minus group coupled with high variability in Glu/Cr concentrations in the plus group.

Consistent with hypothesized predictions, there was a statistically significant group x region interaction in GABA/Cr concentrations, $F(2,25) = 15.86, p < 0.0001$. Yet, contrary to predictions, this difference was driven by a larger GABA/Cr ratio in the plus group compared to the minus group in the PCL, $F(1,11) = 4.40, p = 0.05$, (Figure 6B). There was no between-group difference in GABA/Cr concentrations in the ACC, $F(1,13) = 2.17, p = 0.16$.

As glutamate and GABA respectively represent the major excitatory and inhibitory neurotransmitters in the central nervous system, the ratio of glutamate to GABA is a commonly utilized measure of cortical excitability (Ford, Nibbs, & Crewther, 2017). To investigate between-group differences in cortical excitability, the concentration of total glutamate extracted from the PRESS sequence was divided by total GABA concentrations extracted from the MEGA-PRESS sequence for each group and each region. Overall there was a significant group x region interaction in cortical excitability levels, $F(2,25) = 5.76, p < 0.01$ (Figure 6C). Yet there was no between-group difference in excitability levels in the ACC, $F(1,13) = 1.69, p = 0.22$, or PCL, $F(1,11) = 1.40, p = 0.26$. This finding provides preliminary support, consistent with previous findings in psychosis (Overbeek et al., 2019), for the role of reduced cortical excitability in frontal regions implicated in the neurobiology of psychosis.

Discussion

The present study aimed to investigate the neurobiology of conditioned hallucinations in a healthy undergraduate sample that differed in their propensity to endorse perceptual abnormalities. Overlap in the neural underpinnings of PA in those at risk for psychosis with hallucinations in psychotic illness may provide important insight into the spectrum of psychotic experiences and the pathogenesis that contributes to increased risk for conversion. Consistent with previous research (Powers et al., 2017), hallucinators were more likely to endorse conditioned hallucinations, and were more confident in their responses. Their responses were positively correlated with a measure of hallucinatory experiences, and were not due to between-group differences in detection thresholding. These results provide further support for the predictive coding account of hallucinations and the role of expectation, prior learning, and perceptual knowledge in the etiology of perceptual abnormalities. It demonstrates that hallucinations can be reliably conditioned not only in those with a psychotic illness or personality disorder but also along the continuum of healthy individuals who differed in their propensity for experiencing perceptual aberrations.

Although there was a significant between-group difference in LSHS-R total scores, the two groups did not differ on several measures of schizotypal traits as measured by the SPQ, nor did they differ in mean total scores on the Peters et al. Delusions Inventory or the Chapman Perceptual Aberrations Scale. This may be explained in part by the fully dimensional aspect of the LSHS-R, which assumes that hallucinations exist on a continuum within the normal population (Aleman et al., 2001), compared to the quasi-dimensional approach of the Chapman, which implies that the experience of perceptual abnormalities outside of psychosis represents an at-risk state (Peters et al., 1995) or a slight variant of psychopathology. While the factor

structure of the SPQ is fully dimensional in nature, the LSHS-R may be better suited to capture the specific construct of auditory perceptual abnormalities, whereas there is significant overlap in the constructs measured across various factors of the SPQ. Although the distribution of scores on these measures in the prescreening sample was consistent with previously-reported normative data, the small sample size and large standard deviations of total scores for those included in scanning procedures suggest the benefit of examining these issues further in a larger sample. These findings suggest that the present sample may more closely reflect PA in a healthy young-adult population and may be less representative of an at-risk undergraduate sample. This may be especially helpful for understanding the experience of those who report daily auditory percepts without the associated distress associated with psychotic illness (Pinheiro et al., 2018; Powers et al., 2017).

Contrary to hypothesized predictions, there were no between-group differences in FSIQ, in processing speed, as measured by performance on the Digit-Symbol Substitution Task, or in working memory abilities, as measured by performance on the Letter-Number Sequencing task. These findings are consistent with the previously-noted observation of the current sample perhaps more closely approximating a healthy normative population rather than an at-risk sample. Yet even in help-seeking CHR individuals, there are inconsistent findings on when cognitive deficits emerge, their association with conversion likelihood, and the role of baseline measures in predicting long-term functional outcomes (Bora et al., 2014; Emre Bora & Murray, 2014; Brewer et al., 2006). The most consistent predictive models of conversion risk (Addington, Liu, et al., 2017) include several factors not examined explicitly in the present study including baseline social functioning, bizarre thought content, and disordered communication. Several other studies have also reported no between-group differences in processing speed for both CHR

(Paolo Fusar-Poli et al., 2012) and psychosis samples (Cornelis et al., 2014). The present study also did not measure deficits in social cognition, which some (Piskulic et al., 2016; Shakeel et al., 2019) have noted are more consistent and persistently impaired in CHR individuals over the entire course of the prodromal period.

fMRI results, which should be interpreted cautiously, were also consistent with previous findings on the neurobiology of conditioned hallucinations (Powers et al., 2017). Hallucinators demonstrated decreased activation in the ACC during correct rejections and increased activation during conditioned hallucinations. Decreased ACC engagement during correct rejections suggests that even when not experiencing aberrant percepts, hallucinators struggled with accurate reality monitoring (Wang et al., 2005), perhaps driven the overweighting of top-down prior perceptual learning. ACC activation has also been associated with perceptual learning related to conflict monitoring (Yeung & Nieuwenhuis, 2009), which is negatively correlated with error likelihood. Lower ACC activation patterns are associated with high levels of conflict and higher cognitive demand in decision-making tasks. This provides additional support for the ACC's involvement in the weighting of prediction error during perceptual learning. The ACC is also critical for cognitive control (Barber & Carter, 2005; Lesh, Niendam, Minzenberg, & Carter, 2011) and the inhibition of prepotent responses, suggesting that lower activation in hallucinators may indicate less inhibitory control. Notably, group differences in activation were not observed at other detection threshold levels. Collectively, these findings tentatively provide preliminary support for the overweighting of top-down priors in conditioned hallucinations. While whole-brain analysis demonstrated activation in regions previously reported in symptom-capture fMRI studies of AVH (Zmigrod et al., 2016) and conditioned hallucinations (Powers et al., 2017), the

small sample size limited statistical correction, resulting small cluster sizes and small effect sizes. A larger sample is required to fully interpret these initial results.

There was a higher ratio of glutamate to creatine in the STP+ group compared to the STP- group in the ACC, consistent with hypothesized predictions. These differences were not observed in a control region, providing preliminary support for altered glutamatergic functioning in the neurobiology of conditioned hallucinations. This finding is consistent with previous meta-analyses of MRS studies (Marsman et al., 2013; Merritt, Egerton, Kempton, Taylor, & McGuire, 2016; Poels et al., 2014). The current results are not confounded by methodological factors that have likely contributed to mixed findings across previous MRS studies, such as the impact of medications, (none of the participants reported current psychotropic medication use), or differences in the percent of white matter and CSF across participants. The PRESS sequencing technique used in the present study has strong reliability (Baeshen et al., 2019; Yahya et al., 2008) and utilized a well-established preprocessing pipeline (Simpson et al., 2017). Altered glutamatergic signaling in prefrontal regions including the ACC has been tied to hallucinations and psychotic symptoms more broadly across CHR, first-episode, and chronic samples. This is the first study to demonstrate NMDA-R hypofunction in conditioned hallucinations, suggesting strong overlap in the neurobiology of perceptual abnormalities and providing support for a dimensional approach in linking neurobiology to clinical phenomenology.

While there was a significant group by region interaction in ratio of GABA to total creatine, this was driven by between-group differences in the control region with no group differences in the ACC. Similarly, a significant group by region difference in cortical excitability was not associated with between-group differences in the ACC. This may have been driven by the higher variability of GABA/Cr concentrations within both groups, combined with a lower

sample due to several participants not being able to complete full MRS scanning procedures. Meta-analyses of GABA levels in frontal regions have reported mixed results, with one study finding no differences between psychosis patients (Egerton et al., 2017) and healthy controls and a more recent, larger study reporting reduced GABA levels in the ACC of patients with psychosis (Kumar et al., 2020). Null findings in GABA concentration differences have also been reported in those at ultra-high risk for psychosis (Modinos et al., 2018). While cortical excitability has been associated with schizotypal traits (Ford et al., 2017) and cognitive abilities in first-episode patients (Overbeek et al., 2019), the current sample did not differ on any SPQ factors or total scores, nor did they differ in cognitive abilities. It is likely that the role of altered GABAergic functioning in psychotic experiences may be most relevant for understanding systems-level dysfunction and the interaction of frontal regions with other regions putative to pathogenesis of psychosis, including subcortical and temporal cortical regions (de Jonge et al., 2017; McCutcheon et al., 2020). A longitudinal study (Modinos et al., 2018) following CHR individuals over the course of three years report baseline differences in the correlation of prefrontal GABA levels with regional cerebral blood flow in the hippocampus. Importantly, this association predicted conversion to psychosis. Future studies with multi-site samples may benefit from measuring GABA concentrations both within and across networks associated with NMDA hypofunction.

The current study has several important limitations. Although both behavioral and neuroimaging results are consistent with results from Powers and colleagues (2017), the small sample size and large within-group variability suggest a highly cautious interpretation. It is likely that the current sample reflects the healthier end of the psychosis spectrum and therefore may not be generalizable to help-seeking at-risk clinical samples. Although the two groups differed in

their LSHS-R scores, this is unsurprising given that the measure was used to categorize participants as being high or low in their experience of perceptual abnormalities. It will be important for future studies of non-help-seeking young adult samples to reproduce the reliability of the LSHS-R in measuring hallucinations through administration of similar measures with strong psychometric properties. The PCL was chosen as a control region during MRS procedures as it is not implicated in the neurobiology of conditioned hallucinations, nor is it consistently activated in fMRI studies of auditory hallucinations. However, some studies report increased PCL activation in patients with auditory verbal hallucinations, and the region may be involved in critical for predictive coding. In addition to behavioral and neuroimaging results, computational modeling using a hierarchical gaussian filter approach is required to confirm whether confidence in reporting conditioned hallucinations is associated with the overweighting of top-down prior beliefs, consistent with predictive coding theory of hallucinations. Although some studies (Mathalon et al., 2019) suggest a low precision of priors in the etiology of auditory verbal hallucinations, this may be specifically relate to the auditory system's strong bias for speech and differential disruption of priors at different hierarchical levels from lower sensory cortices to higher-level order associative cortices (Sterzer et al., 2018). MRS measures both inactive and active metabolite concentrations, and the majority of physiologically active glutamate is derived from glutamine (Rowland et al., 2013). Future studies should also examine between-group differences in glutamine to determine whether Glu/Cr differences may be biased by measurement of extracellular inactive glutamate.

The current study aimed to build upon previous investigations of the predictive coding account of hallucinations by examining conditioned hallucinations in healthy, college-aged individuals who differ in their propensity toward endorsing perceptual aberrations and linking

the phenomenology of these experiences with the well-established role of prefrontal NMDA hypofunction in the neurobiology of hallucinations. STP+ individuals were more likely to endorse conditioned hallucinations and were more confident in their responses, which was associated with differences in ACC activation and Glu/Cr concentrations, but not GABA/Cr concentrations nor differences in cortical excitability. Consistent with previous findings of conditioned hallucinations (Powers et al., 2017) and predictive coding accounts of psychosis (Horga et al., 2014; Ranson et al., 2019; Sterzer et al., 2018; Teufel et al., 2015), these results require replication in a larger sample and application of computational techniques to determine whether these effects are driven by the overweighting of top-down prior beliefs. This is the first study to replicate the conditioned hallucination effect within the “healthy end” of the psychosis continuum, and the first study limited to college-aged individuals, a population that is important for broad-based screening efforts in the early detection and prevention of psychotic illnesses. While narrow in scope and limited in generalizability, the current study extends previous efforts (Corlett et al., 2009; Kapur, 2003) to conceptualize the phenomenology of hallucinations and its underlying neurobiology within a cognitive, computational framework. Continued efforts in this direction will be critical for not only further characterizing these symptoms, but also for developing new treatment modalities and biological targets that can improve the lives of those with psychosis.

Appendices

Figure 1. PRISMA Diagram of Participant Recruitment.

Demographic	STP + Group	STP – Group	<i>p</i> value (Chi-Square or T-test)
N	6	10	--
Age (years)	20.14 (0.60)	20.82 (2.45)	0.80
Sex (% Female)	66.66%	70.00%	1.00
Ethnicity	66.6% White 33.3% Black	90% White 10% Asian	0.14
Sexual Orientation	83.3% Heterosexual	90% Heterosexual	0.79
Years of Education	13.5 (0.9)	13.1 (1.3)	0.82
FSIQ, Mean (SD)	100 (10)	108 (11)	0.19

Table 1. Phase B Participant Demographics. N= number of participants, FSIQ= Full-Scale Intelligence Quotient. *P* value represents results of either Chi-Square or independent samples t-test.

Survey Measure	STP + Group (N=6)	STP – Group (N=10)	<i>p</i> value
Total LSHS-R Score	29.00 (6.87)	9.10 (7.23)	< 0.001
Total PDI Score	54.83 (24.20)	37.75 (16.18)	0.14
Total SPQ Score	28.17 (15.83)	17.10 (14.26)	0.19
SPQ Perceptual Aberrations	2.83 (2.64)	1.10 (1.29)	0.10
SPQ Cognitive Perceptual	10.17 (7.17)	7.00 (6.00)	0.36
Chapman Total Score	7.83 (6.74)	7.00 (4.99)	0.78
DSST T-Score	53.83 (5.95)	58.10 (6.21)	0.20
LNS T-Score	49.33 (3.33)	56.40 (10.99)	0.15

Table 2. Phase B Self-Report and Cognitive Testing Results.

LSHS-R= Launay-Slade Hallucination Scale Revised; PDI= Peters Delusion Inventory;
SPQ= Schizotypal Personality Questionnaire; Chapman = Chapman Perceptual Aberration Scale;
DSST= Digit Symbol Substitution Task; LNS= Letter Number Sequencing Task

SPQ Cognitive-Perceptual Factor Clinical Cutoffs (N=242)

Figure 2: Participant Pool Survey Results. Violin Plot comparison of all eligible participants total scores on the Cognitive-Perceptual factor (CP) of the Schizotypal Personality Questionnaire (SPQ) and the Chapman Perceptual Aberration Scale. Red line indicates the mean SPQ- CP total score in patients with psychosis while the blue line represents SPQ-CP mean in healthy individuals (Raine, 1991).

Figure 3. Task Behavioral Data. There was no significant between-group difference in the detection threshold (dBSNR) levels (3A). The two groups differed in the probability of responding yes when no tone was presented, but there were no such differences in the probability of responding yes at the 25%, 50%, or 75% of the detection threshold (3B). The probability of responding yes to no tone correlated significantly with the LSHS-R total score (3C). The two groups differed in the level of confidence in “yes” versus “no” responses during the no tone condition, but this difference was not apparent at any other detection threshold level (3D). *n.s.* = not significant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

Figure 4: Whole-Brain fMRI Results by Condition. Whole-brain analysis was conducted to determine activation during conditioned hallucinations. Cluster-based correction was utilized with a height threshold of $p < .001$ and cluster threshold of $p < .05$. Few clusters survived correction and all were small ($k < 20$) in size. Results shown for when participants responded “yes” to no-tone trials (conditioned hallucinations, 4A) and for differences between responding “yes” versus “no” to no-tone trials (4B). Tables indicates size of cluster (*k*), peak coordinates (*x*, *y*, *z*), and magnitude of the effect (*Z*).

Figure 5: Region of Interest (ROI) fMRI Results by Condition. ROI analysis was conducted to determine activation in the main region of interest of the study, the anterior cingulate (ACC), as well as in the control region, the paracentral lobule (PCL) during the conditioned hallucinations task. In the right ACC ($x = -8, y = -32, z = 6$) there were several regions that demonstrated higher levels of activation during “yes” responses to no-tone trials (5A). There was also some activation in the right PCL ($x = -7, y = -32, z = 53$) during this condition (5B). There was also increased activation when comparing “yes” responses to “no” responses in both the right ACC (5C) and right PCL (5D) but the magnitude of these differences was smaller.

6A: Ratio of Glutamate to Total Creatine

6B: Ratio of GABA to Total Creatine

6C: Ratio of Glutamate to GABA (Cortical Excitability)

Figure 6. Magnetic Resonance Spectroscopy Results. Concentrations of total glutamate (ppm) as a ratio to total creatine concentrations (ppm) were higher in the anterior cingulate cortex (ACC) voxel for the STP Plus (plus) group compared to the STP Minus (minus) group but there was no between-group difference in the paracentral lobule (PCL) control voxel (6A). There was a significant group x region interaction in the concentrations of total GABA (ppm) as a percent of total creatine (ppm) concentration driven by a larger GABA/Cr ratio in the plus group than the minus group in the control region (6B). There was a significant group by region interaction in cortical excitability as measured by the ratio of glutamate to GABA in the two regions (6C). *n.s.* = not significant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

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