Emotional Experience, Paranoia, and Probabilistic Reasoning in Schizophrenia

by

Tyler B. Grove

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Psychology)
in The University of Michigan
2018

Doctoral Committee:

Professor Patricia J. Deldin, Co-Chair
Assistant Professor Ivy F. Tso, Co-Chair
Professor Cindy Lustig
Professor Stephan F. Taylor

Tyler B. Grove

tylerg@umich.edu

ORCID iD: 0000-0003-4227-5072

DEDICATION

This dissertation is dedicated to my wife and family for their unconditional love and support, and to all of my mentors who have provided invaluable guidance and support throughout my graduate school experience. I have been fortunate enough to be surrounded by kind, caring, intelligent, and thoughtful people who enriched my life and always encouraged me to pursue my goals.

ACKNOWLEDGMENTS

Graduate school can really test your mettle. You find out pretty quick what you're made of; your flaws and strengths are exacerbated. Graduate school requires you to exercise those strengths and patch up your flaws. That is exactly the kind of life experience I wanted. To be challenged and learn not only how to be a researcher and clinician, but also to test my mettle and see if I can grow as a person. While I did experience some sleeplessness worrying about my study designs, scrambled to meet grant deadlines or stay late to finish patient notes, and spent many hours processing data and rewriting manuscripts, I also experienced the pride of a (fairly) sound study design, submitting a proposal, helping patients overcome by stress, and publishing a manuscript in a scientific journal. It hasn't been easy, but I would not have learned anything if it were, and that's the point of graduate school. You learn and in turn use that acquired skill set and knowledge to help others. I am now ready and excited to help others, and that makes it all worthwhile.

There is a long list of people who I would like to thank for their support and guidance throughout graduate school. Below is that list.

First, I would like to thank my advisor and mentor, Dr. Patricia Deldin, for her confidence in my ability to become a clinical scientist. I feel truly fortunate to have Dr. Deldin has my mentor. She has always encouraged creative and critical thinking, and whenever I felt as though I was moving off course, she was there to steer me in the right direction, and it has been a privilege and honor to work with her.

Without Dr. Ivy Tso guiding me through a 12-year process of first becoming a competent undergraduate research assistant, then study coordinator, and finally graduate student clinician and researcher, I would not be where I am today. Dr. Tso is a statistical expert, skilled clinician, amazing writer, and caring mentor. I have been fortunate that our paths crossed when I was an undergraduate and I am excited to continue working with Dr. Tso as a post-doc.

Dr. Steve Taylor for encouraging my advancement in the field of psychology. Dr. Taylor allowed me to start working in his lab as an undergraduate student and then recommended me for a study coordinator position all while encouraging me to pursue graduate school.

Dr. Vicki Ellingrod for her support and encouragement throughout my time as her study coordinator and then graduate school applicant. Dr. Ellingrod was instrumental in my preparation for graduate school.

Dr. Savanna Mueller for being my partner in crime as we conducted multiple studies with memorable acronyms. I'll truly cherish our time together as graduate student researchers.

Drs. Sara Konrath and Brad Bushman for taking a chance and agreeing to be my undergraduate honors thesis mentors. That was my introduction to research and I could not have been in better hands.

Dr. Cindy Lustig for joining my dissertation committee and being patient and supportive throughout the process.

Chris Broussard and Igor Belopski for their invaluable coding skills. Without these two genius coders I would not have any dissertation tasks.

My team of undergraduate research assistants are the ground troops who make research possible. I've been fortunate to work with many wonderful students over the

past four years, including Lauren, Andrea, Becca, Dayna, Shiren, Nicole, Hannah, Mariam, Wisteria, Nathan, Diana, Chelsea, Lauren, Beier, and Alex. Thank you for all of your hard work and dedication to each projection.

I would like to thank my research funding sources, including UM Rackham Graduate Student Research Grants, the UM Psychology Department Dissertation Award, and the Blue Cross Blue Shield Student Grant.

Finally, I would not have been able to complete graduate school without my wife, she was always a calming and supportive presence throughout the process, and my family for always providing support and encouragement throughout my life.

PREFACE

This dissertation aimed to better understand cognitive and affective processes linked to distress and poor functional outcomes in schizophrenia by examining emotional experience, paranoia, and reasoning. The basis of this research stemmed from my passion to develop novel treatments and/or enhance current treatments for the millions of people diagnosed with schizophrenia. All research questions were formulated together with my advisor, Dr. Patricia Deldin. Each study was designed and conducted in collaboration with Dr. Deldin, who also provided supervision and consultation throughout the duration of each study. All data were collected between 2006 and 2017. I was engaged in researching and writing this dissertation from April 2016 to April 2018. This dissertation was also completed to fulfill the Ph.D. graduation requirements of the University of Michigan Rackham Graduate School. With my doctorate, it is my hope that I am able to continue answering research questions as a competent clinical scientist and that my research, and the research of others, may one day help those with schizophrenia see improvements in their quality of life.

TABLE OF CONTENTS

CHAPTER

LIST OF TABLES

TABLE

LIST OF FIGURES

FIGURE

ABSTRACT

Schizophrenia (SZ) is a chronic mental disorder characterized by longstanding and severe social functioning deficits. In trying to better understand psychosocial factors that perpetuate these functional deficits, this dissertation included three studies that examine cognitive and affective factors with the potential to improve functional outcomes in SZ: 1) emotional experience, 2) paranoia, and 3) reasoning. Study one examined negative/positive affect and social functioning with self-report measures among SZ, affective disorders, and the general population. Study 2 assessed paranoia and its relationship with the interpretation of the environment via affective sound localization in SZ. Study 3 compared probabilistic reasoning when estimating the likely source of threatening and non-threatening affective stimuli while also examining the relationship between probabilistic reasoning and delusional thinking in SZ. The findings of this dissertation suggest that for people with schizophrenia: 1) treatment of heightened negative affect and reduced positive affect may improve social functioning, 2) paranoia may aid localization of natural sounds that occur in the environment, and 3) promoting more conservative probabilistic reasoning may help to reduce delusional thinking.

CHAPTER 1

Overview

Psychosis is a disconnection from reality that can manifest as paranoid and delusional thinking. This type of thinking occurs when people firmly hold false beliefs. Delusional thinking appears in varying severity, ranging from one of the most debilitating diseases in the world, schizophrenia (WHO, 2004), to 10-15% of the general population who experience regular delusions and minimal functional impairment (Freeman et al., 2007). In line with the transdiagnostic framework of the NIMH Research Domain Criteria (RDoC) Initiative, this pattern suggests that delusional thinking may exist along a dimension and is not specific to a serious mental illness.

Delusional thinking is associated with excess dopamine transmission in the reward system regions of the brain. Dopamine plays a significant role in the prediction of novel rewards and identification of salient stimuli. Abnormal dopamine transmission alters these processes and leads to an aberrant sense of novelty and inappropriate assignment of salience to insignificant events that can result in the formation of false paranoid beliefs (e.g., a stranger briefly staring at you may be misinterpreted as a threat; Morrison & Murray, 2009).

As such, treatment for psychosis has traditionally consisted of dopamine antagonists called antipsychotic medications, which target delusional thinking via blockage of excess dopamine receptors in the brain (Kapur, Agid, Mizrahi, & Li, 2006). While antipsychotic medications can be effective in managing delusions, up to 30% of people with a psychosis do not respond to these medications (Ackenheil & Weber, 2004). Further, the metabolic side effects of antipsychotic medications may contribute to high rates of non-compliance (Dibonaventura, Gabriel, Dupclay, Gupta, & Kim, 2012), as individuals experience weight gain and increased risk for cardiovascular disease (Tschoner et al., 2007). While social functioning may improve with continued use of antipsychotic medications, most individuals do not return to premorbid levels of functioning with these medications alone (Chien & Yip, 2013). In response to concerns of antipsychotic side effects, compliance, and effectiveness, cognitive-behavioral therapy for psychosis (CBTp) has emerged as an empirically supported treatment for psychotic symptoms (e.g., delusional thinking) across diagnostic groups (e.g., delusional thinking, Mehl, Werner, & Lincoln, 2015). Evidence suggests that treatment with CBTp may help regulate dopamine transmission in the brain similar to antipsychotics (Bell et al., 2008; Cervenka et al., 2012). CBTp is based on Beck's cognitive model of psychopathology in which biased processing of events/stimuli promotes a distorted interpretation of these experiences and leads to maladaptive emotional and behavioral responses (Beck, 1963, 2005). In psychosis, the combination of biased thinking, negative emotions, and maladaptive behaviors may interact to perpetuate delusional thinking (Mueser, Deavers, Penn, & Cassisi, 2013). For example, the sound of a neighbor walking through one's yard late at night may be interpreted as a salient event and hastily misinterpreted as a suspicious act. A delusional thought that this neighbor is a spy may arise due to overestimation of the current limited evidence (i.e., neighbor is walking through the yard). This perceived threat might lead to the evocation of negative affect that helps to reinforce the belief (e.g., "I feel fear and anxiety so this person is a threat") and behavioral changes such as avoiding neighbors. Repeated avoidance results in missed opportunities to challenge this hasty conclusion and can lead to an intractable delusional and paranoid thought (e.g., my neighbor is a spy). Within the CBTp model, a cycle of paranoia, biased thinking and reasoning (e.g., overestimation of improbable events), misinterpretation of environmental/social stimuli, and negative emotions may help to explain the chronic social functioning deficits observed in serious mental illnesses. In particular, mundane social interactions may be negatively misinterpreted and considered stressful events (Myin-Germeys et al., 2003) that elicit heightened negative affect, along with biased and delusional/paranoid thinking and incautious reasoning (Sarin & Wallin, 2014).

Within this cognitive model, the contribution of emotional experience towards delusional thinking and social functioning is particularly striking considering the high prevalence and frequency of negative emotions and lack of positive emotions reported in people with psychosis compared with healthy controls (Gruber, Eidelman, Johnson, Smith, & Harvey, 2011; Horan, Blanchard, Clark, & Green, 2008; Kring & Moran, 2008; Myin-Germeys, Delespaul, & deVries, 2000; Oorschot et al., 2013; Rowland et al., 2013; Tso, Grove, & Taylor, 2014). Negative and positive affect are related to both clinical outcomes (e.g., delusional thinking), functional outcomes (Dinzeo, Cohen, Nienow, & Docherty, 2008; Docherty et al., 2011; McCleery et al., 2012), and the interpretation of neutral stimuli as threatening in people with psychosis (Underwood, Kumari, & Peters, 2016). Thus, emotional experience is associated with biased interpretations of the environment (i.e., misinterpretation of threat) and appears to play a role in functional outcomes within psychosis (van Rossum, Dominguez, Lieb, Wittchen, & van Os, 2011).

As such, one of the aims of CBTp is to challenge biased thinking and reasoning prior to the experience of elevated negative affect and formation of delusions. By challenging biases (e.g., collecting evidence for and against a conclusion; utilizing cautious reasoning), CBTp may help to reduce the heightened neural and negative emotional response to threatening stimuli (Kumari et al., 2011; Mason, Peters, Dima, Williams, & Kumari, 2016). Yet, despite this evidence for CBTp effectiveness (Kane et al., 2016), meta-analyses show small effect sizes for CBTp in people with psychosis ($g = -0.33$) when comparing overall symptoms before and after treatment (Jauhar et al., 2014). It is possible that the cognitive model of CBTp may be enhanced with a greater ecological understanding of paranoid thinking and biased reasoning, along with emotional experience, within serious mental illnesses. Further exploration of emotions and biases within social and affective contexts may help to enhance our understanding of critical CBTp treatment targets. For instance, while people with schizophrenia have shown deficits in the ability to accurately interpret the environment via impaired sound localization accuracy (Balogh, 1979; Perrin, 2010), it is currently unknown if sound localization deficits vary by the affect elicited by sounds that may be heard within the natural environment (e.g., someone laughing). In addition, it is unknown if paranoia is associated with the ability to interpret the environment via sound localization in people with schizophrenia. Finally, few studies have determined if probabilistic reasoning varies between neutral and affective contexts. Moreover, a transdiagnostic approach may yield a broader understanding of emotional experience, as a relationship between social functioning impairment and heightened negative affect and reduced positive affect across diagnoses would suggest a unified treatment protocol for affect.

The present dissertation includes three studies that examines emotional experience and social functioning, paranoid thinking and the interpretation of the environment, and probabilistic reasoning of affective stimuli in people with a serious mental illness.

The first study seeks to determine if negative affect is associated with social functioning across groups, ranging from healthy individuals to mood disorders and psychotic disorders. An integrated data analysis was used that incorporates self-report measures of negative affect and social functioning from five studies at the University of Michigan, one online study, and one multi-site study that includes Harvard University, Columbia University, University of Texas Southwestern Medical Center, and the University of Michigan. Within clinical populations, we examined the incremental contribution of negative affect towards social functioning with respect to traditional predictors that include positive/negative symptoms, non-social cognition, and social cognition.

The second study examined the relationship between paranoia and the emotional reaction to- and spatial localization of- environmental stimuli. A sound localization paradigm was used in people with schizophrenia and healthy individuals. Participants provided valence/arousal ratings for each environmental sound in addition to localizing these sounds. Sound localization performance was compared by individual and standardized valence/arousal ratings of stimuli. Levels of paranoia and neurocognition were assessed.

The third study explores probabilistic reasoning that may contribute to a specific cognitive bias robustly associated with delusional thinking in people with psychosis (i.e., jumping to conclusions). This study used two versions of a probabilistic reasoning task, with one version using only neutral stimuli and the other using affective stimuli (i.e., threatening and non-threatening). Differences in probabilistic reasoning will be compared by evidence type (i.e., disconfirmatory or confirmatory), salience of stimuli (threatening or non-threatening), and by group (i.e. schizophrenia or healthy control). The relationship between probabilistic reasoning and delusional thinking was examined.

The results of this dissertation may help to guide future research aimed at enhancing the effectiveness of CBTp interventions for people with a serious mental illness.

Specific Aims

1. Determine if emotional experience (i.e., negative and positive affect) is associated with social functioning across serious mental illnesses and non-clinical populations.
2. Determine the relationship between paranoia and the affective reaction to- and localization of- auditory environmental stimuli in people with schizophrenia.
3. Examine probabilistic reasoning style during an affective paradigm using threatening and non-threatening stimuli in people with schizophrenia.

References

Ackenheil, M., & Weber, K. (2004). Differing response to antipsychotic therapy in schizophrenia: pharmacogenomic aspects. *Dialogues in Clinical Neuroscience, 6*(1), 71-77.

Beck, A. T. (1963). Thinking and Depression. I. Idiosyncratic Content and Cognitive Distortions. *Arch Gen Psychiatry, 9*, 324-333.

Beck, A. T. (2005). The current state of cognitive therapy: a 40-year retrospective. *Arch Gen Psychiatry, 62*(9), 953-959. doi:10.1001/archpsyc.62.9.953

Bell, C., Bhika, S., Porter, R., Frampton, C., Carter, J., McIntosh, V., . . . Joyce, P. (2008). The response to sulpiride in major depression before and after cognitive behavioural therapy: D2 receptor function. *Acta Neuropsychiatrica, 20*(04), 199-206. doi:doi:10.1111/j.1601-5215.2008.00284.x

Cervenka, S., Hedman, E., Ikoma, Y., Djurfeldt, D. R., Ruck, C., Halldin, C., & Lindefors, N. (2012). Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder. *Transl Psychiatry, 2*, e120. doi:10.1038/tp.2012.40

Chien, W. T., & Yip, A. L. (2013). Current approaches to treatments for schizophrenia spectrum disorders, part I: an overview and medical treatments. *Neuropsychiatr Dis Treat, 9*, 1311-1332. doi:10.2147/NDT.S37485

Dibonaventura, M., Gabriel, S., Dupclay, L., Gupta, S., & Kim, E. (2012). A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatry, 12*, 20. doi:10.1186/1471-244X-12-20

Dinzeo, T. J., Cohen, A. S., Nienow, T. M., & Docherty, N. M. (2008). Arousability in schizophrenia: relationship to emotional and physiological reactivity and symptom severity. *Acta Psychiatrica Scandinavica, 117*(6), 432-439. doi:10.1111/j.1600-0447.2008.01185.x

Docherty, N. M., St-Hilaire, A., Aakre, J. M., Seghers, J. P., McCleery, A., & Divilbiss, M. (2011). Anxiety interacts with expressed emotion criticism in the prediction of psychotic symptom exacerbation. *Schizophrenia Bulletin, 37*(3), 611-618. doi:10.1093/schbul/sbp123

Freeman, D., Garety, P. A., Kuipers, E., Fowler, D., Bebbington, P. E., & Dunn, G. (2007). Acting on persecutory delusions: the importance of safety seeking. *Behav Res Ther, 45*(1), 89-99. doi:10.1016/j.brat.2006.01.014

Gruber, J., Eidelman, P., Johnson, S. L., Smith, B., & Harvey, A. G. (2011). Hooked on a feeling: Rumination about positive and negative emotion in inter-episode bipolar disorder. *Journal of Abnormal Psychology, 120*(4), 956-961.

Horan, W. P., Blanchard, J. J., Clark, L. A., & Green, M. F. (2008). Affective traits in schizophrenia and schizotypy. *Schizophr Bull, 34*(5), 856-874. doi:10.1093/schbul/sbn083

Jauhar, S., McKenna, P. J., Radua, J., Fung, E., Salvador, R., & Laws, K. R. (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry, 204*(1), 20-29. doi:10.1192/bjp.bp.112.116285

Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., . . . Heinssen, R. K. (2016). Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. *American Journal of Psychiatry, 173*(4), 362-372. doi:10.1176/appi.ajp.2015.15050632

Kapur, S., Agid, O., Mizrahi, R., & Li, M. (2006). How antipsychotics work-from receptors to reality. *NeuroRx, 3*(1), 10-21.

Kring, A. M., & Moran, E. K. (2008). Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull, 34*(5), 819-834. doi:10.1093/schbul/sbn071

Kumari, V., Fannon, D., Peters, E. R., Ffytche, D. H., Sumich, A. L., Premkumar, P., . . . Kuipers, E. (2011). Neural changes following cognitive behaviour therapy for psychosis: a longitudinal study. *Brain, 134*(Pt 8), 2396-2407. doi:10.1093/brain/awr154

Mason, L., Peters, E. R., Dima, D., Williams, S. C., & Kumari, V. (2016). Cognitive Behavioral Therapy Normalizes Functional Connectivity for Social Threat in Psychosis. *Schizophrenia Bulletin, 42*(3), 684-692. doi:10.1093/schbul/sbv153

McCleery, A., Divilbiss, M., St-Hilaire, A., Aakre, J. M., Seghers, J. P., Bell, E. K., & Docherty, N. M. (2012). Predicting social functioning in schizotypy: an investigation of the relative contributions of theory of mind and mood. *Journal of Nervous and Mental Disease, 200*(2), 147-152. doi:10.1097/NMD.0b013e3182439533

Mehl, S., Werner, D., & Lincoln, T. M. (2015). Does Cognitive Behavior Therapy for psychosis (CBTp) show a sustainable effect on delusions? A meta-analysis. *Frontiers in Psychology, 6*, 1450. doi:10.3389/fpsyg.2015.01450

Morrison, P. D., & Murray, R. M. (2009). From real-world events to psychosis: the emerging neuropharmacology of delusions. *Schizophrenia Bulletin, 35*(4), 668-674. doi:10.1093/schbul/sbp049

Mueser, K. T., Deavers, F., Penn, D. L., & Cassisi, J. E. (2013). Psychosocial treatments for schizophrenia. *Annu Rev Clin Psychol, 9*, 465-497. doi:10.1146/annurev-clinpsy-050212-185620

Myin-Germeys, I., Delespaul, P., & deVries, M. W. (2000). Schizophrenia patients are more emotionally active than is assumed based on their behavior. *Schizophrenia Bulletin, 26*(4), 847-854.

Myin-Germeys, I., Peeters, F., Havermans, R., Nicolson, N. A., DeVries, M. W., Delespaul, P., & Van Os, J. (2003). Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatr Scand, 107*(2), 124-131.

Oorschot, M., Lataster, T., Thewissen, V., Lardinois, M., Wichers, M., van Os, J., . . . Myin-Germeys, I. (2013). Emotional experience in negative symptoms of schizophrenia--no evidence for a generalized hedonic deficit. *Schizophr Bull, 39*(1), 217-225. doi:10.1093/schbul/sbr137

Rowland, J. E., Hamilton, M. K., Lino, B. J., Ly, P., Denny, K., Hwang, E. J., . . . Green, M. J. (2013). Cognitive regulation of negative affect in schizophrenia and bipolar disorder. *Psychiatry Res, 208*(1), 21-28. doi:10.1016/j.psychres.2013.02.021

Sarin, F., & Wallin, L. (2014). Cognitive model and cognitive behavior therapy for schizophrenia: an overview. *Nord J Psychiatry, 68*(3), 145-153. doi:10.3109/08039488.2013.789074

Tschoner, A., Engl, J., Laimer, M., Kaser, S., Rettenbacher, M., Fleischhacker, W. W., . . . Ebenbichler, C. F. (2007). Metabolic side effects of antipsychotic medication. *International Journal of Clinical Practice, 61*(8), 1356-1370. doi:10.1111/j.1742-1241.2007.01416.x

Tso, I. F., Grove, T. B., & Taylor, S. F. (2014). Differential hedonic experience and behavioral activation in schizophrenia and bipolar disorder. *Psychiatry Res, 219*(3), 470-476. doi:10.1016/j.psychres.2014.06.030

Underwood, R., Kumari, V., & Peters, E. (2016). Cognitive and neural models of threat appraisal in psychosis: A theoretical integration. *Psychiatry Res, 239*, 131-138. doi:10.1016/j.psychres.2016.03.016

van Rossum, I., Dominguez, M. D., Lieb, R., Wittchen, H. U., & van Os, J. (2011). Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. *Schizophr Bull, 37*(3), 561-571. doi:10.1093/schbul/sbp101

WHO. (2004). *Global Burden of Disease 2004*: World Health Organization.

CHAPTER 2

Study 1. Emotional experience and social functioning in psychotic disorders, bipolar disorder, major depressive disorder, and non-clinical groups

Abstract

Evidence suggests that emotional experience contributes to functional outcomes in severe mental illnesses. Yet, it is unknown if the strength of this relationship differs within mental illnesses compared with the general population. This cross-sectional study expands upon previous work by examining emotional experience (i.e., negative and positive affect) as a predictor of social functioning in a large sample of clinical and non-clinical groups. A total of 1,118 participants from six clinical studies at the University of Michigan and a national multi-site study diagnosed with a psychotic disorder, bipolar disorder, or major depressive disorder, along with healthy controls and a crowdsourcing sample, completed self-report measures of negative affect (e.g., State-Trait Anxiety Inventory and Beck Depression Inventory) and positive affect (e.g., Differential Emotions Scale). These measures predicted social functioning with medium to large effect sizes (r = 0.35 to 0.80 for negative affect; r = -0.28 to -0.59 for positive affect) even after controlling for “traditional” predictors of outcomes that include demographics, cognition or intelligence, positive symptoms, negative symptoms, and/or mania within each group. Accordingly, the results suggest that emotional experience is a critical dimension of functioning across mental illnesses and the general population.

Introduction

Severe mental illnesses such as schizophrenia, bipolar disorder, and major depressive disorder are characterized by chronic deficits in social functioning. Research suggests that emotional experience in the form of heightened negative affect (e.g., sadness and anxiety) and decreased positive affect (e.g., calmness and confidence) may contribute to these social functioning deficits. A relationship between affect and functioning could exist across disorders, including schizophrenia, as people with schizophrenia report heightened negative affect and decreased positive affect (Havermans, Nicolson, Berkhof, & deVries, 2010; Hofmann & Meyer, 2006; Kring & Moran, 2008; Oorschot et al., 2013) that is related to social functioning (Kohler & Martin, 2006). Despite this potential relationship, emotional experience has traditionally been overlooked in schizophrenia (Kring & Caponigro, 2010).

In light of the National Institute of Mental Health Research Domain Criteria Initiative (RDoC; Insel et al., 2010) in which dimensions of functioning (e.g., cognition and behavior) are examined across traditional categories of mental disorders and those without psychopathology, emotional experience could be considered such a dimension across both clinical and general populations, with heightened negative affect and reduced positive affect in psychopathology that warrants treatment. Elevated negative affect and reduced positive affect may contribute to social functioning deficits in schizophrenia and bipolar disorder above and beyond cognitive deficits, positive symptoms, or negative symptoms (Grove et al., 2016; Tso, Grove, & Taylor, 2010). However, it is currently unknown if this pattern is distinctly different or stronger within groups of psychopathologies compared with the general population. It is possible that the contribution of emotional experience towards social functioning is specific to categories of mental illnesses and/or is a dimension of functioning relevant to the general population and those without psychopathology. Further, it is unknown if the functional role of both negative and positive affect is independent of “traditional” predictors of outcome (e.g., neurocognition) across this wide range of populations.

Thus, the primary goals of the current study are to: (1) examine levels of negative and positive affect in a range of clinical and non-clinical samples using self-report measures, (2) identify potential differences in levels of negative and positive affect as a function of clinical diagnosis, and (3) determine if levels of negative and positive affect explain a significant amount of variance in social functioning among all participants and within each diagnostic group before and after accounting for traditional functional predictors, including neurocognition or general intelligence, social cognition, positive symptoms (e.g., hallucinations), negative symptoms (e.g., anhedonia), mania, and/or demographics. We predicted that elevated negative affect and reduced positive affect would be present in all clinical samples (i.e., major depressive disorder [MDD], bipolar disorder [BD], and schizophrenia and other psychotic disorders [SOPD]) compared with healthy controls (HC) and the general population (i.e., online crowdsourcing sample via Amazon mechanical Turk [M-Turk]). We also predicted that, within each sample, a significant amount of variance in social functioning would be explained by each measure of negative and positive affect, even after accounting for traditional functional predictors. Ultimately, the findings may provide justification for unified psychosocial interventions (Bullis et al., 2015) that aim to reduce negative affect and promote positive affect in order to improve social functioning in severe mental illnesses.

Methods

Participants

We aggregated cross-sectional data collected from: 1) six separate University of Michigan studies in the Departments of Psychology and Psychiatry and College of Pharmacy, 2) a four-site study Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC; Trivedi et al., 2016) that included the University of Michigan, Columbia University, McLean Hospital/Massachusetts General Hospital/Harvard Medical School, and the University of Texas Southwestern Medical Center, and 3) the Amazon Mechanical Turk (M-Turk) online crowdsourcing platform, which provided a diverse sample more representative of the general population than traditional convenience samples such as undergraduate subject pools, along with comparable reliability (Behrend, Sharek, Meade, & Wiebe, 2011; Buhrmester, Kwang, & Gosling, 2011). Taken together, the study included 1,118 participants, with 718 participants having a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) Axis I diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, bipolar disorder I, bipolar disorder II, bipolar disorder not otherwise specified, or major depressive disorder as verified by the patient version of the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997) or the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994). In addition, 142 participants had no history of a DSM-IV Axis I diagnosis verified by the non-patient version of the SCID-IV (First et al., 1997). A total of 257 participants completed measures online via M-Turk and provided self-report diagnosis of a mental illness but did not complete assessments of cognition or symptoms. A total of 329 participants (healthy control = 84; psychotic disorder not otherwise specified = 21; schizoaffective = 105; and schizophrenia = 119) were part of a previous report that also focused on negative affect and social functioning (Grove et al., 2016). Since participants did not complete the same measures across studies, participants were organized into groups based on diagnosis or sample origin to include the maximal number of participants based on available data (i.e., healthy controls [HC], M-Turk participants [M-Turk], major depressive disorder [MDD], bipolar disorders [BD], and schizophrenia and other psychotic disorders [SOPD]). See Table 1 for measures available, sample size, and diagnoses per group.

Self-report measures

Negative affect

Six self-report measures were used to assess levels of negative affect: 1) State subscale of the State-Trait Anxiety Inventory (STAI-S; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), 2) Revised version of the Beck Depression Inventory (BDI-IA; Beck & Steer, 1987), 3) Negative emotions subscale of the modified version of the Differential Emotions Scale (DES-N; Fredrickson, Tugade, Waugh, & Larkin, 2003), 4) Psychological Stress Index (PSI; Tso, Grove, & Taylor, 2012), 5) Negative affect subscale of the state version of the Positive and Negative Affect Schedule (PANAS-N; Watson, Clark, & Tellegen, 1988), and/or 6) General Distress Subscale of the 30-item version of the Mood and Anxiety Symptom Questionnaire (MASQ-GD; Nitschke, Heller, Imig, McDonald, & Miller, 2001; Wardenaar et al., 2010).

Positive affect

Three self-report measures were used to assess levels of positive affect: 1) Positive emotion subscale of the modified version of the Differential Emotions Scale (DES-P; Fredrickson et al., 2003), 2) Positive affect subscale of the state version of the Positive and Negative Affect Schedule (PANAS-P; Watson et al., 1988), and/or 3) Anhedonic Depression Subscale of the 30-item version of the Mood and Anxiety Symptom Questionnaire, which measures a lack of positive affect and thus was reverse scored (MASQ-AD; Nitschke et al., 2001).

Social functioning

The Social Adjustment Scale – Self-Report (SAS-SR; Weissman, 1999) was used to assess social functioning. SAS-SR includes six domains of functioning: 1) work role, 2) social and leisure, 3) family outside the home, 4) primary relationship, 5) parental, and 6) family unit. SAS-SR has demonstrated a strong relationship with the clinician-rated Global Assessment of Functioning scale in SZ (Wittorf, Wiedemann, Buchkremer, & Klingberg, 2008) and has been used in BD (Sentissi et al., 2008) and MDD (Dunn et al., 2012). Only participants enrolled in EMBARC completed the abbreviated 24-item version of the SAS-SR (Gameroff, Wickramaratne, & Weissman, 2012). Higher scores indicate poorer social functioning.

Other self-report

The Altman Self-Rating of Mania (ASRM; Altman, Hedeker, Peterson, & Davis, 1997) was used to assess mania.

Clinical ratings and Medications

Positive symptoms of psychosis were assessed with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). Negative symptoms of psychosis were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a). Daily chlorpromazine (CPZ) equivalents in milligrams were determined for participants taking antipsychotic medications (Woods, 2003, 2011) are available in Supplemental Table 1, along with use of antidepressants, anxiolytics, and mood stabilizers.

Neuropsychological assessments

The Brief Assessment of Cognition (BACS; Keefe et al., 2004) or Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was used to assess general neurocognitive function or intelligence, respectively, according to the individual study protocols. The Managing Emotions branch of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT-ME; Mayer, Salovey, & Caruso, 1999) was used to assess social cognition.

Data analyses

To reduce the number of analyses, *z*-scores of negative and positive affect measures for each participant were computed and then averaged for each group's unique combination of available measures (e.g., negative affect composite *z*-score for M-Turk participants consisted of the average of BDI-IA, STAI-S, DES-N, and PANAS-N *z*-scores). Composite negative and positive affect *z*-score, along with each negative/positive self-report measure, clinical measures, and demographics, were compared between groups via one-way analysis of variance (ANOVA). Tukey HSD was used for all post-hoc ANOVA analyses. Table 2 provides all demographic and clinical differences between groups. Chi-square was used to assess differences in demographics and psychotropic medication use between groups. A simple *t*-test was used to determine differences in daily CPZ equivalents between BD and SOPD (Supplemental Table 1). Internal consistency of self-report measures was determined with Cronbach's alpha. Self-report measures demonstrated good to excellent internal consistency ($\alpha = 0.82$ to 0.95) among all participants, including M-Turk participants. Pearson correlation analysis was used to determine relationships between social functioning (SAS-SR), "traditional" functional predictors (i.e., neurocognition or general intelligence, social cognition, positive symptoms, negative symptoms, manic symptoms, and/or age, sex, and level of education), individual measures of negative/positive affect, and daily CPZ equivalents in milligrams. Pearson correlation analysis was also used to determine the relationship between social functioning and composite negative/positive affect *z*-score in each group. Fisher *r*-to-*z* transformation was used to determine group differences between these Pearson correlations.

Simple regression models were used to examine the relationship between SAS-SR and negative/positive composite *z*-score, along with each individual measure of negative/positive affect, in each group. Hierarchical regression analysis was used to predict SAS-SR variance with composite negative/positive affect *z*-score above and beyond traditional predictors of functioning within each group. Using a separate multiple regression analysis with demographic variables predicting SAS-SR among all participants, only significant demographic predictors of SAS-SR, along with other traditional predictors, were entered into Step 1 of the hierarchical regression analyses for each group. The composite negative or positive affect *z*-score was placed into Step 2 of all the group regression models, resulting in two regression models for each group.

These hierarchical regression analyses were also repeated with each individual measure of negative/positive affect within in each group.

Results

Significant correlations were observed between SAS-SR and all measures of affect (Figure 1). All self-report measures of negative and positive affect were significantly correlated with one another among all participants (Supplemental Table 2).

Figure 2 shows that the correlation between SAS-SR and composite negative or positive affect was significant in all groups. For negative affect composite, when conducting pairwise comparisons between these correlations using Fisher *r*-to-*z* transformation, HC and MDD shared the weakest correlation and BD had the strongest correlation. M-Turk and SOPD were intermediate to these groups. For positive affect composite, MDD had the weakest correlation compared with all other groups.

Hierarchical regression analyses showed that composite negative/positive affect *z*-score each predicted SAS-SR variance after controlling for available “traditional” variables in HC, MDD, BD, and SOPD (Table 3). These findings were replicated using each raw individual measure of negative/positive affect (Supplemental Table 3). The significant demographic differences observed between the groups (Table 2), provided justification for a separate multiple regression analysis (i.e., age, sex, and level of education predicting SAS-SR among all participants) to determine which demographic variables to include in Step 1 of the hierarchical regression analyses. Level of education and sex but not age significantly predicted composite negative affect variance, p’s < 0.01. Level of education but not age or sex significantly predicted composite positive affect variance, $p < 0.001$. Thus, only level of education was entered into Step 1 of the hierarchical regression analyses (sex was also included for negative affect only). Simple regression models showed that composite negative/positive affect *z*-score, along with each individual negative/positive affect measure, significantly predicted SAS-SR variance (Supplemental Table 4).

One-way ANOVA and Tukey HSD post-analysis showed that composite levels of negative affect were significantly elevated in MDD, BD, and SOPD compared with HC. M-Turk participants were intermediate to HC and clinical groups. Composite levels of positive affect were significantly reduced in MDD, BD, and SOPD compared with HC. M-Turk participants were again intermediate to HC and clinical groups (Figure 3).

Discussion

The current study examined the relationship between self-reported negative and positive affect and social functioning in people diagnosed with a major depressive disorder, bipolar disorder, psychotic disorder, along with an unselected online crowdsourcing sample to represent the general population and people with no history of a mental illness (*N* = 1,118). While the highest levels of negative affect and lowest levels of positive affect were observed in those diagnosed with a mental illness, both negative and positive affect explained significant amounts of variance in social functioning across all groups (up to 50%). Levels of negative and positive affect also explained a significant amount of social functioning variance above and beyond the available “traditional” predictors of functioning that include neurocognition or general intelligence, social cognition, positive symptoms, negative symptoms, mania, and/or demographics. Thus, affect appears to be a significant predictor of self-reported social functioning across the continuum between psychopathology and heath.

The current findings show comparable emotional experience of negative and positive affect between MDD, BD, and SOPD, along with a strong link between affect and social functioning. Heightened negative affect and reduced positive affect have been identified as critical components in the pharmacological and/or psychosocial treatment of MDD (Michels, 1997; Oren-Yagoda, Bjorgvinsson, & Aderka, 2017), with a lack of positive emotions being a discriminative characteristic of MDD compared with anxiety disorders (Eysenck & Fajkowska, 2017). For SOPD and BD, treatment of heightened negative affect or reduced positive affect (e.g., depression) may be focused on pharmacology (Parker, Graham, & Tavella, 2017) and most people with a severe mental illness do not receive psychosocial treatments (Ince, Haddock, & Tai, 2016; Lehman & Steinwachs, 1998; Moran, 2003). As an adjunct to pharmacology, unified psychosocial treatment protocols (Taylor, Lyubomirsky, & Stein, 2017) for reducing negative affect and increasing positive affect across affective and psychotic disorders may help to improve social functioning.

Heightened negative affect and reduced positive affect in mental illnesses compared with non-clinical samples may be explained by heightened stress sensitivity—a reduced ability to tolerate minor stressors that often results in the experience of negative emotions (Myin-Germeys et al., 2003). Stress sensitivity has been linked to the pathophysiology and risk of MDD (Bogdan, Nikolova, & Pizzagalli, 2013; Wichers et al., 2009), BD (Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006), and schizophrenia (Corcoran et al., 2012). Stress sensitivity in these disorders may be linked to dysregulation of the physiological response (e.g., heightened cortisol levels) to stress via the hypothalamic-pituitary-adrenal (HPA) axis (Steen et al., 2014; Steen et al., 2011; Zimmerman, Bellaire, Ewing, & Grace, 2013). Yet, the causal relationship between HPA axis dysregulation and negative affect is unknown and complicated by findings of blunted cortisol in schizophrenia during a task that putatively elicits negative affect (i.e., Trier Social Stress Test (Zorn et al., 2017). A similar question arises with negative affect and social functioning in terms of causality (i.e., it is unknown if negative affect causes social functioning impairment or the reverse). While emotional experience is a predictor of social functioning in schizophrenia (Tso et al., 2010), if a cycle of negative affect (possibly associated with stress sensitivity and HPA axis abnormalities) and social functioning impairment exists, targeting emotional experience could help to weaken this cycle regardless of an established causal relationship between affect and social functioning. In contrast, those without a mental illness or subthreshold psychiatric symptoms may demonstrate resiliency towards minor stressors. Unified psychosocial treatment protocols could help patients build sustainable coping skills to manage distressing symptoms and events that may lead to negative affect (Smith, Nathan, Juniper, Kingstep, & Lim, 2003) and promote behavioral activation (Mazzucchelli, Kane, & Rees, 2010) to increase positive affect. However, before such protocols are developed, future investigations of the psychosocial mechanisms of negative affect across normal functioning and psychopathology are needed prior to confirm appropriate treatment targets (e.g., stress sensitivity).

The strong correlations observed between measures of depression, anxiety, psychological stress, general distress, anhedonic depression, and frequency of negative and positive emotions suggests that these measures may tap into a single latent factor known as emotional experience (i.e., negative and positive affect). Previous reports have also shown strong correlations between measures of depression (BDI) and anxiety (STAI; Block, 1991; Nitschke et al., 2001) along with derivation of a latent variable of negative affect using the BDI and Beck Anxiety Inventory in clinical populations (Clark, Steer, & Beck, 1994). A comprehensive package of negative and positive affect measures used across a large sample of clinical and non-clinical participants would allow for the confirmation of this latent variable via factor analysis, as partially overlapping samples made factor analysis inappropriate due to the small ratio of sample size to variables in the current study.

The relationship between social functioning and available measures of negative affect (STAI-S and MASQ) or positive affect (MASQ) was weakest in MDD compared with BD and SOPD, despite MDD reporting higher levels of depression, state anxiety, and social functioning impairment than BD and SOPD. It is possible that MDD is more heterogeneous than BD and SOPD in terms of personality profiles that carry unique levels of functional impairment (Hori et al., 2017). Thus, the relationship between affect and social functioning may be weaker in MDD. For this reason, treatment of MDD may be most effective when individually targeting both depressive symptoms and functional impairments (Sheehan, Nakagome, Asami, Pappadopulos, & Boucher, 2017). It is possible that stratification of MDD according to personality profiles would yield subgroups with a stronger relationship between affect and social functioning. However, the use of the abbreviated version of the SAS-SR in MDD only, along with the relatively limited number of affect measures in MDD, may have limited the examination of this relationship in the current study.

The M-Turk sample reported higher levels of negative affect and social functioning impairment than HC and were intermediate to those with a severe mental illness and HC. This finding suggests that M-Turk participants may not be “normal” or representative of the psychiatrically healthy population. Considering the growing use of M-Turk for non-clinical research (Chandler & Shapiro, 2016; Pauszek, Sztybel, & Gibson, 2017), emotional experience and social functioning may need to be considered when interpreting findings of such research. Nevertheless, the addition of the M-Turk sample falls in the subclinical range of the psychopathology-healthy continuum and is typically a more representative sample of the general population than traditional convenience samples such as undergraduate subject pools (e.g., older; more ethnically diverse and more life experiences; Behrend et al., 2011; Buhrmester et al., 2011).

Limitations of the current study include the use of self-report measures, as memory function (Kuswanto, Sum, & Sim, 2013) and cognitive biases (Strauss & Gold, 2012) influence the accuracy of self-reports. Since the time interval for the self-report measures used in this study ranged from the current moment (STAI-S) to the past month (PSI), measures with a reduced reliance on memory may be better suited to assess negative affect. However, similar self-report measures of social functioning and negative affect have demonstrated adequate internal consistency and/or test-retest reliability in studies of schizophrenia and bipolar disorder (Baumstarck et al., 2013; Leidy, Palmer, Murray, Robb, & Revicki, 1998; Ma et al., 2014; Trivedi et al., 2004), and are highly correlated with clinician estimates, which have the advantage of utilizing both patient report and behavioral observations (Voruganti, Heslegrave, Awad, & Seeman, 1998). Self-report measures also demonstrate predictive validity, as self-reported negative affect predicts objective outcome measures such as the number of 12-month interval hospitalizations in schizophrenia (Tso et al., 2012). Thus, self-reports provide critical, reliable, and valid assessment of negative affect and social functioning (Bellack et al., 2007). Future studies would benefit from independent assessments of social functioning in addition to a self-report measures to confirm concurrent validity. In addition, psychotropics (e.g., antidepressants) may reduce stress reactivity (Jacobson, 2014), and in turn reduce negative affect. Thus, levels of negative affect in the current study may have been higher in the absence of psychotropics. However, the idiosyncratic patient response to medications (not just antidepressants) is difficult to control for practically and theoretically, making it difficult to draw conclusions regarding medications, affect, and social functioning. Further, the cross-sectional nature of the current study limits the determination of casual relationships. The use of an online crowdsourcing platform limited the ability to clinically assess M-Turk participants and might have the problem of selection bias, limiting the generalizability of the findings from this part of the sample in the current study.

To conclude, negative and positive affect were highly predictive of social functioning independent of neurocognition or general intelligence, social cognition, positive symptoms, negative symptoms, mania, and/or demographics in people with a major depressive disorder, bipolar disorder, schizophrenia or other psychotic disorder, an unselected online crowdsourcing sample, and people with no history of mental illness. The findings suggest that emotional experience is a critical dimension relevant to social functioning regardless of diagnosis or presence of mental illness. Thus, targeting emotional experience with empirically-supported interventions may improve social functioning in clinical populations.

References

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Keyser, J., & Gerstein, R. K. (2006). A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Dev Psychopathol, 18*(4), 1055-1103. doi:10.1017/S0954579406060524

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman Self-Rating Mania Scale. *Biological Psychiatry, 42*(10), 948-955. doi:10.1016/S0006-3223(96)00548-3

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Andreasen, N. C. (1984a). *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa.

Andreasen, N. C. (1984b). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa.

Baumstarck, K., Boyer, L., Boucekine, M., Aghababian, V., Parola, N., Lancon, C., & Auquier, P. (2013). Self-reported quality of life measure is reliable and valid in adult patients suffering from schizophrenia with executive impairment. *Schizophr Res, 147*(1), 58-67. doi:10.1016/j.schres.2013.03.008

Beck, A. T., & Steer, R. A. (1987). *Manual for the Beck Depression Inventory, 1993 edition*. San Antonio, TX: The Psychological Corporation.

Behrend, T. S., Sharek, D. J., Meade, A. W., & Wiebe, E. N. (2011). The viability of crowdsourcing for survey research. *Behav Res Methods, 43*(3), 800-813. doi:10.3758/s13428-011-0081-0

Bellack, A. S., Green, M. F., Cook, J. A., Fenton, W., Harvey, P. D., Heaton, R. K., . . . Wykes, T. (2007). Assessment of community functioning in people with schizophrenia and other severe mental illnesses: a white paper based on an NIMH-sponsored workshop. *Schizophr Bull, 33*(3), 805-822. doi:10.1093/schbul/sbl035

Block, P. (1991). Measurement and intercorrelations of psychiatric symptomatology in inpatients. *Psychological Reports, 68*, 1055-1056.

Bogdan, R., Nikolova, Y. S., & Pizzagalli, D. A. (2013). Neurogenetics of depression: a focus on reward processing and stress sensitivity. *Neurobiol Dis, 52*, 12-23. doi:10.1016/j.nbd.2012.05.007

Buhrmester, M., Kwang, T., & Gosling, S. D. (2011). Amazon's Mechanical Turk: A New Source of Inexpensive, Yet High-Quality, Data? *Perspect Psychol Sci, 6*(1), 3-5. doi:10.1177/1745691610393980

Bullis, J. R., Sauer-Zavala, S., Bentley, K. H., Thompson-Hollands, J., Carl, J. R., & Barlow, D. H. (2015). The unified protocol for transdiagnostic treatment of emotional disorders: preliminary exploration of effectiveness for group delivery. *Behav Modif, 39*(2), 295-321. doi:10.1177/0145445514553094

Chandler, J., & Shapiro, D. (2016). Conducting Clinical Research Using Crowdsourced Convenience Samples. *Annu Rev Clin Psychol, 12*, 53-81. doi:10.1146/annurev-clinpsy-021815-093623

Clark, D. A., Steer, R. A., & Beck, A. T. (1994). Common and specific dimensions of self-reported anxiety and depression: implications for the cognitive and tripartite models. *J Abnorm Psychol, 103*(4), 645-654.

Corcoran, C. M., Smith, C., McLaughlin, D., Auther, A., Malaspina, D., & Cornblatt, B. (2012). HPA axis function and symptoms in adolescents at clinical high risk for schizophrenia. *Schizophr Res, 135*(1-3), 170-174. doi:10.1016/j.schres.2011.11.035

Dunn, T. W., Vittengl, J. R., Clark, L. A., Carmody, T., Thase, M. E., & Jarrett, R. B. (2012). Change in psychosocial functioning and depressive symptoms during acute-phase cognitive therapy for depression. *Psychol Med, 42*(2), 317-326. doi:10.1017/S0033291711001279

Eysenck, M. W., & Fajkowska, M. (2017). Anxiety and depression: toward overlapping and distinctive features. *Cogn Emot*, 1-10. doi:10.1080/02699931.2017.1330255

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version, Administration Booklet*: American Psychiatric Press.

Fredrickson, B. L., Tugade, T. M., Waugh, C. E., & Larkin, G. R. (2003). What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. *Journal of Personality and Social Psychology, 84*(2), 365-376.

Gameroff, M. J., Wickramaratne, P., & Weissman, M. M. (2012). Testing the Short and Screener versions of the Social Adjustment Scale-Self-report (SAS-SR). *Int J Methods Psychiatr Res, 21*(1), 52-65. doi:10.1002/mpr.358

Grove, T. B., Tso, I. F., Chun, J., Mueller, S. A., Taylor, S. F., Ellingrod, V. L., . . . Deldin, P. J. (2016). Negative affect predicts social functioning across schizophrenia and bipolar disorder: Findings from an integrated data analysis. *Psychiatry Res, 243*, 198-206. doi:10.1016/j.psychres.2016.06.031

Havermans, R., Nicolson, N. A., Berkhof, J., & deVries, M. W. (2010). Mood reactivity to daily events in patients with remitted bipolar disorder. *Psychiatry Res, 179*(1), 47-52. doi:10.1016/j.psychres.2009.10.020

Hofmann, B. U., & Meyer, T. D. (2006). Mood fluctuations in people putatively at risk for bipolar disorders. *Br J Clin Psychol, 45*(Pt 1), 105-110. doi:10.1348/014466505X35317

Hori, H., Teraishi, T., Nagashima, A., Koga, N., Ota, M., Hattori, K., . . . Kunugi, H. (2017). A personality-based latent class typology of outpatients with major depressive disorder: association with symptomatology, prescription pattern and social function. *J Affect Disord, 217*, 8-15. doi:10.1016/j.jad.2017.03.053

Ince, P., Haddock, G., & Tai, S. (2016). A systematic review of the implementation of recommended psychological interventions for schizophrenia: Rates, barriers, and improvement strategies. *Psychol Psychother, 89*(3), 324-350. doi:10.1111/papt.12084

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D., Quinn, K., . . . Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research of mental disorders. *Am J Psychiatry, 167*(7).

Jacobson, L. (2014). Hypothalamic-pituitary-adrenocortical axis: neuropsychiatric aspects. *Compr Physiol, 4*(2), 715-738. doi:10.1002/cphy.c130036

Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res, 68*(2-3), 283-297. doi:10.1016/j.schres.2003.09.011

Kohler, C. G., & Martin, E. A. (2006). Emotional processing in schizophrenia. *Cogn Neuropsychiatry, 11*(3), 250-271. doi:10.1080/13546800500188575

Kring, A. M., & Caponigro, J. M. (2010). Emotion in Schizophrenia: Where Feeling Meets Thinking. *Curr Dir Psychol Sci, 19*(4), 255-259. doi:10.1177/0963721410377599

Kring, A. M., & Moran, E. K. (2008). Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull, 34*(5), 819-834. doi:10.1093/schbul/sbn071

Kuswanto, C. N., Sum, M. Y., & Sim, K. (2013). Neurocognitive Functioning in Schizophrenia and Bipolar Disorder: Clarifying Concepts of Diagnostic Dichotomy vs. Continuum. *Front Psychiatry, 4*, 162. doi:10.3389/fpsyt.2013.00162

Lehman, A., & Steinwachs, D. M. (1998). At Issue: Translating Research Into Practice: The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations. *Schizophrenia Bulletin, 24*(1), 1-10.

Leidy, N. K., Palmer, C., Murray, M., Robb, J., & Revicki, D. A. (1998). Health-related quality of life assessment in euthymic and depressed patients with bipolar disorder. Psychometric performance of four self-report measures. *J Affect Disord, 48*(2-3), 207-214.

Ma, X. R., Hou, C. L., Zang, Y., Jia, F. J., Lin, Y. Q., Li, Y., . . . Xiang, Y. T. (2014). Could the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) be used in depressed schizophrenia patients? *Journal of Affective Disorders, 172C*, 191-194. doi:10.1016/j.jad.2014.09.051

Mayer, J. D., Salovey, P., & Caruso, D. R. (1999). *Mayer-Salovey-Caruso Emotional Intelligence Test*. North Tonawanda, NY: Multi-Health Systems Inc.

Mazzucchelli, T. G., Kane, R. T., & Rees, C. S. (2010). Behavioral activation interventions for well-being: A meta-analysis. *J Posit Psychol, 5*(2), 105-121. doi:10.1080/17439760903569154

Michels, R. (1997). Psychotherapeutic approaches to the treatment of anxiety and depressive disorders. *J Clin Psychiatry, 58 Suppl 13*, 30-32.

Moran, M. (2003). *Psychosocial treatments rare for schizophrenia patients*. Retrieved from

Myin-Germeys, I., Peeters, F., Havermans, R., Nicolson, N. A., DeVries, M. W., Delespaul, P., & Van Os, J. (2003). Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatr Scand, 107*(2), 124-131.

Nitschke, J. B., Heller, W., Imig, J. C., McDonald, R. P., & Miller, G. A. (2001). Distinguishing dimensions of anxiety and depression. *Cognitive Therapy and Research, 25*(1), 1-22. doi:10.1016/j.jad.2011.10.005

Nurnberger, J. I., Jr., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., . . . Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry, 51*(11), 849-859; discussion 863-844.

Oorschot, M., Lataster, T., Thewissen, V., Lardinois, M., Wichers, M., van Os, J., . . . Myin-Germeys, I. (2013). Emotional experience in negative symptoms of schizophrenia--no evidence for a generalized hedonic deficit. *Schizophr Bull, 39*(1), 217-225. doi:10.1093/schbul/sbr137

Oren-Yagoda, R., Bjorgvinsson, T., & Aderka, I. M. (2017). The relationship between positive affect and negative affect during treatment for major depressive disorder. *Psychother Res*, 1-11. doi:10.1080/10503307.2017.1292066

Parker, G. B., Graham, R. K., & Tavella, G. (2017). Is there consensus across international evidence-based guidelines for the management of bipolar disorder? *Acta Psychiatr Scand, 135*(6), 515-526. doi:10.1111/acps.12717

Pauszek, J. R., Sztybel, P., & Gibson, B. S. (2017). Evaluating Amazon's Mechanical Turk for psychological research on the symbolic control of attention. *Behav Res Methods*. doi:10.3758/s13428-016-0847-5

Sentissi, O., Navarro, J. C., De Oliveira, H., Gourion, D., Bourdel, M. C., Bayle, F. J., . . . Poirier, M. F. (2008). Bipolar disorders and quality of life: the impact of attention deficit/hyperactivity disorder and substance abuse in euthymic patients. *Psychiatry Res, 161*(1), 36-42. doi:10.1016/j.psychres.2007.06.016

Sheehan, D. V., Nakagome, K., Asami, Y., Pappadopulos, E. A., & Boucher, M. (2017). Restoring function in major depressive disorder: A systematic review. *J Affect Disord, 215*, 299-313. doi:10.1016/j.jad.2017.02.029

Smith, L., Nathan, P., Juniper, U., Kingstep, P., & Lim, L. (2003). Cognitive Behavioural Therapy for Psychotic Symptoms: A Therapist's Manual. In R. a. T. Centre for Clinical Interventions: Psychotherapy (Ed.). Perth, Australia.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Steen, N. E., Methlie, P., Lorentzen, S., Dieset, I., Aas, M., Nerhus, M., . . . Andreassen, O. A. (2014). Altered systemic cortisol metabolism in bipolar disorder and schizophrenia spectrum disorders. *Journal of Psychiatric Research*. doi:10.1016/j.jpsychires.2014.01.017

Steen, N. E., Methlie, P., Lorentzen, S., Hope, S., Barrett, E. A., Larsson, S., . . . Andreassen, O. A. (2011). Increased systemic cortisol metabolism in patients with schizophrenia and bipolar disorder: a mechanism for increased stress vulnerability? *J Clin Psychiatry, 72*(11), 1515-1521. doi:10.4088/JCP.10m06068yel

Strauss, G. P., & Gold, J. M. (2012). A new perspective on anhedonia in schizophrenia. *Am J Psychiatry, 169*(4), 364-373. doi:10.1176/appi.ajp.2011.11030447

Taylor, C. T., Lyubomirsky, S., & Stein, M. B. (2017). Upregulating the positive affect system in anxiety and depression: Outcomes of a positive activity intervention. *Depress Anxiety, 34*(3), 267-280. doi:10.1002/da.22593

Trivedi, M. H., McGrath, P. J., Fava, M., Parsey, R. V., Kurian, B. T., Phillips, M. L., . . . Weissman, M. M. (2016). Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. *J Psychiatr Res, 78*, 11-23. doi:10.1016/j.jpsychires.2016.03.001

Trivedi, M. H., Rush, A. J., Ibrahim, H. M., Carmody, T. J., Biggs, M. M., Suppes, T., . . . Kashner, T. M. (2004). The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med, 34*(1), 73-82.

Tso, I. F., Grove, T. B., & Taylor, S. F. (2010). Emotional experience predicts social adjustment independent of neurocognition and social cognition in schizophrenia. *Schizophr Res, 122*(1-3), 156-163. doi:10.1016/j.schres.2009.12.007

Tso, I. F., Grove, T. B., & Taylor, S. F. (2012). Self-assessment of psychological stress in schizophrenia: Preliminary evidence of reliability and validity. *Psychiatry Res, 195*(1-2), 39-44. doi:10.1016/j.psychres.2011.07.009

Voruganti, L., Heslegrave, R., Awad, A. G., & Seeman, M. V. (1998). Quality of life measurement in schizophrenia: reconciling the quest for subjectivity with the question of reliability. *Psychol Med, 28*(1), 165-172.

Wardenaar, K. J., van Veen, T., Giltay, E. J., de Beurs, E., Penninx, B. W., & Zitman, F. G. (2010). Development and validation of a 30-item short adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ). *Psychiatry Res, 179*(1), 101-106. doi:10.1016/j.psychres.2009.03.005

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol, 54*(6), 1063-1070.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence.* New York, NY.: The Psychological Corporation: Harcourt Brace & Company.

Weissman, M. M. (1999). *Social Adjustment Scale (SAS-SR)*. Tonawanda, NY: Multi-Health Systems Inc.

Wichers, M., Geschwind, N., Jacobs, N., Kenis, G., Peeters, F., Derom, C., . . . van Os, J. (2009). Transition from stress sensitivity to a depressive state: longitudinal twin study. *Br J Psychiatry, 195*(6), 498-503. doi:10.1192/bjp.bp.108.056853

Wittorf, A., Wiedemann, G., Buchkremer, G., & Klingberg, S. (2008). Prediction of community outcome in schizophrenia 1 year after discharge from inpatient treatment. *Eur Arch Psychiatry Clin Neurosci, 258*(1), 48-58. doi:10.1007/s00406-007-0761-z

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry, 64*(6), 663-667.

Woods, S. W. (2011). *Chlorpromazine Equivalent Doses for Atypical Antipsychotics: An Update 2003-2010*. Psychiatry. Yale University. http://scottwilliamwoods.com.

Zimmerman, E. C., Bellaire, M., Ewing, S. G., & Grace, A. A. (2013). Abnormal stress responsivity in a rodent developmental disruption model of schizophrenia. *Neuropsychopharmacology, 38*(11), 2131-2139. doi:10.1038/npp.2013.110

Zorn, J. V., Schur, R. R., Boks, M. P., Kahn, R. S., Joels, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology, 77*, 25-36.

Acknowledgements

This research was partially supported by the National Institute of Mental Health of the National Institutes of Health under award numbers U01MH092221 and U01MH092250, National Institutes of Health (5KL2TR000434-08 and 5K23MH108823), University of Michigan Rackham Graduate Student Research Grant, American Psychological Foundation Benton-Meier Neuropsychology Scholarship, National Institute of Mental Health (R01MH064148, R01MH082784, and R21MH086701), The Heinz C. Prechter Research Program and Richard Tam Foundation, Palenscar Research Fund, National Center for Research Resources, General Clinical Research Center Program (UL1RR024986), and Chemistry Core of Diabetes Research and Training Center (NIH5P60 DK 20572). In addition, Dr. Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehreinger Ingelheim, Pfizer, and Posit Science for activities unrelated to the present work. The current findings were presented at the Society for Research in Psychopathology 2016 Meeting in Baltimore, Maryland, USA.

Table 2.1: Summary of diagnoses and measures within each group (*N*=1,118)

	HC (*n*=142)	M-Turk (*n*=257)	MDD (*n*=279)	BD (*n*=195)	SOPD (*n*=245)
(a) Diagnosis					
Psychotic disorders					
Schizophrenia		3 (1%)			119 (49%)
Schizoaffective disorder					105 (43%)
Psychotic disorder NOS					21 (9%)
Bipolar disorders		3 (1%)			
Bipolar I disorder				148 (76%)	
Bipolar II disorder				30 (15%)	
Bipolar disorder NOS				1 (0%)	
Depression		28 (11%)			
Major depressive disorder, single episode			36 (13%)		
Major depressive disorder, recurrent			237 (85%)		
Anxiety		23 (9%)			
PTSD, Personality disorder, or other		7 (3%)			
No psychiatric diagnosis	142 (100%)	191 (74%)			
No diagnosis specifier provided		2 (1%)	6 (2%)	16 (8%)	
(b) Measures					
Neurocognition (BACS)	✗			✗	✓
General intelligence (WASI)	✗		✓	✗	
Social cognition (MSCEIT-ME)	✗			✓	✗
Positive symptoms (SAPS)				✗	✗
Negative symptoms (SANS)				✗	✗
Mania (ASRM)				✓	✗
Positive affect					
DES-P	✗	✓		✗	✗
PANAS-P		✓		✗	
MASQ-AD	✗		✓		
Negative affect					
STAI-S	✓	✓	✓	✓	✗
BDI-IA	✗	✓		✓	✓
DES-N	✗	✓		✓	✗
PSI	✗			✓	✓
PANAS-N		✓		✗	
MASQ-GD	✗		✓		
Social functioning (SAS-SR)	✓[a]	✓	✓[a]	✓	✓

Note. Blank = not collected. × = not collected for all. ✓ = collected for all. * = diagnoses are self-reported. [a] = some or all participants completed the abbreviated version of the Social Adjustment Scale – Self-Report (SAS-SR). HC = healthy control. M-Turk = Amazon Mechanical Turk participants. MDD = Major depressive disorder. BD = Bipolar disorders. SOPD = Schizophrenia and other psychotic disorders. NOS = Not otherwise specified. PTSD = Post-traumatic stress disorder. BACS = Brief Assessment of Cognition in Schizophrenia. WASI = Wechsler Abbreviated Scale of Intelligence. MSCEIT-ME = Managing Emotions subscale of the Mayer-Salovey-Caruso Emotional Intelligence Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. ASRM = Altman Self-Rating Mania Scale. DES-P = positive emotions subscale of the modified version of the Differential Emotions Scale. PANAS-P = The Positive Affect subscale of the Positive and Negative Affect Schedule. MASQ-AD = Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire. STAI-S = state subscale of the State-Trait Anxiety Index. BDI-IA = revised version of the Beck Depression Inventory. DES-N = negative emotion subscale of the modified version of the Differential Emotions Scale. PSI = Psychological Stress Index. PANAS-N = The Negative Affect subscale of the Positive and Negative Affect Schedule. MASQ-GD = General Distress subscale of the 30-item version of the Mood and Anxiety Questionnaire. SAS-SR = Social Adjustment Scale – Self-Report.

Table 2.2: Demographic, cognitive, clinical, and functional characteristics of all participants (*N* = 1,118)

		HC (*n*=142)	M-Turk (*n*=257)	MDD (*n*=279)	BD (*n*=195)	SOPD (n=245)	Omnibus		Post-hoc
	Scale range	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	χ^2, *F*, or *t*	*p*	Tukey's HSD or χ^2
Age		39.2 (13.5)	36.3 (10.8)	36.9 (13.3)	46.7 (13.2)	43.7 (12.2)	28.93	<.0001	HC, M-Turk, MDD < BD, SOPD
Sex (number of males)		75 (52.8%)	117 (46.1%)	93 (33.3%)	57 (29.7%)	139 (56.7%)	49.83	<.0001	M-Turk, BD < SOPD; MDD < HC, M-Turk, SZ; BD < HC, M-Turk
Education	1-8	5.9 (1.6)	5.7 (0.9)	5.4 (1.8)	5.4 (1.7)	4.1 (1.6)	42.36	<.0001	MDD, BD < HC; SOPD < all
1st language (English/Tamil/ other)			216 / 22 / 19						
Country of origin (USA/India/other)			193 / 57 / 7						
BACS[a]		0.0 (1.0)			-1.2 (1.0)	-2.1 (1.3)	90.39	<.0001	SOPD < BD < HC
WASI[a]		113.7 (12.7)		112.5 (10.7)	108.9 (10.9)		5.63	.004	BD < HC, MDD
MSCEIT-ME[a]		106.7 (19.9)			96.6 (12.0)	91.1 (15.5)	19.15	<.0001	SOPD < BD < HC
SAPS[a]	0-5				0.6 (1.2)	4.4 (3.6)	3.93	.0002	
SANS[a]	0-5				4.1 (3.0)	6.5 (3.9)	3.52	.0006	
ASRM[a]	0-4	1.9 (2.6)			2.5 (3.2)	4.3 (4.0)	3.27	.04	BD < SOPD
SAS-SR[a]	0-5	1.5 (0.3)	1.9 (0.6)	2.6 (0.6)	2.1 (0.6)	2.3 (0.5)	115.89	<.0001	HC < M-Turk < BD, SOPD < MDD

Note. [a]Data not collected for all participants. For level of education, an ordinal ranking was created, with a higher level of education signified by a higher ranking. SES = socioeconomic status. BACS = Brief Assessment of Cognition in Schizophrenia. WASI = Wechsler Abbreviated Scale of Intelligence. MSCEIT-ME = Mayer-Salovey-Caruso Emotional Intelligence Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. ASRM = Altman Self-Rating Mania Scale. SAS-SR = Social Adjustment Scale – Self-Report. M

= mean. SD = standard deviation. HC = healthy control. M-Turk = Amazon Mechanical Turk participants. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders.

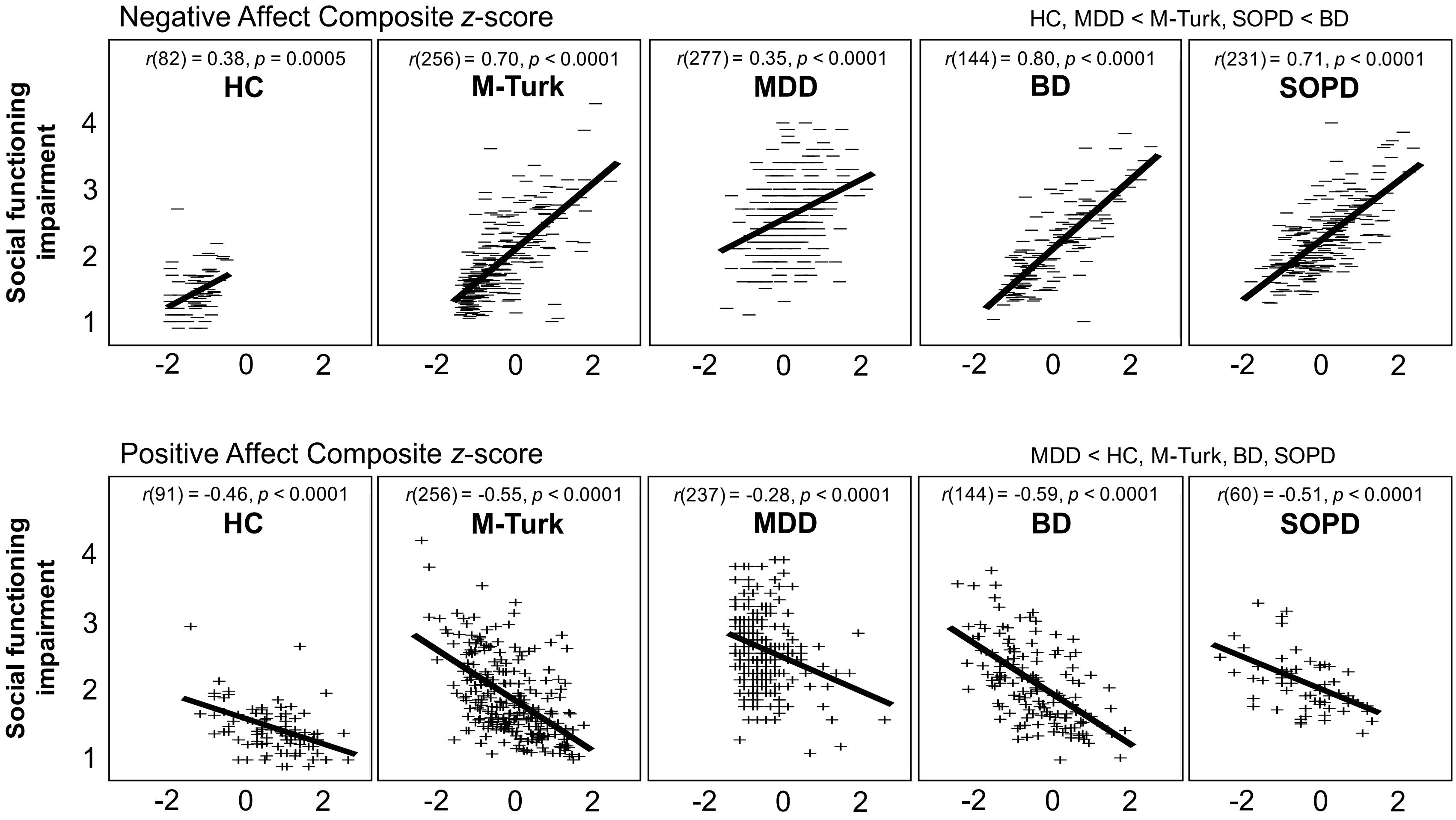
Table 2.3: Hierarchical regression analyses of negative/positive affect composite scores as predictors of social functioning impairment (SAS-SR) variance after controlling for traditional functional predictors within each group

	HC		M-Turk		MDD		BD		SOPD			
	(*n*=40)		(*n*=253)		(*n*=203)		(*n*=134)		V1 (*n*=189)		V2 (*n*=45)	
	Variable	Model	Variable	Model	Variable	Model	Variable	Model	Variable	Model	Variable	Model
	b	ΔR^2	*b*	ΔR^2	*b*	ΔR^2	*b*	ΔR^2	*b*	ΔR^2	*b*	ΔR^2
Step 1 (Model A)												
Level of education	-0.09*	0.05	-0.16*	0.03*	0.08	0.06**	-0.19*	0.27***	-0.03	0.04*	-0.10	0.16
Sex	-0.23		-0.03		0.12		0.18*		0.18*		0.17	
BACS	0.02								-0.09		-0.30	
WASI					-0.23**		-0.19*					
MSCEIT-ME							-0.31***				0.28	
SAPS											0.08	
SANS											0.18	
ASRM							0.12					
Step 2												
Negative affect composite	0.51**	0.20**	0.69***	0.48***	0.33***	0.11***	0.71***	0.41***	0.70***	0.46***	0.76***	0.37***
Step 1 (Model B)									--	--		
Level of education	-0.07	0.01	-0.16*	0.03*	0.08	0.05**	-0.18*	0.24***			-0.03	0.13
BACS	-0.01				-0.24**						-0.30	
WASI							-0.21*					
MSCEIT-ME							-0.26**				0.26	
SAPS							0.10				0.11	
SANS											0.15	
ASRM												
Step 2									--	--		
Positive affect composite	-0.51***	0.25***	-0.55***	0.28***	-0.28***	0.08***	-0.62***	0.31***			-0.51***	0.23***

Note. Sex only included in model for negative affect composite; males coded as 0 and females as 1. Only standardized betas are reported. M-Turk = Amazon Mechanical Turk participants. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders. WASI = Wechsler Abbreviated Scale of Intelligence. BACS = Brief Assessment of Cognition in Schizophrenia. MSCEIT-ME = Managing Emotions subscale of the Mayer-Salovey-Caruso Emotional Intelligence Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. ASRM = Altman Self-Rating Mania Scale. DES-P = positive emotions subscale of the Differential Emotions Scale. MASQ-AD = Anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire. BDI-IA = revised version of the Beck Depression Inventory. PSI = Psychological Stress Index. STAI-S = state subscale of the State-Trait Anxiety Index. DES-N = negative emotion subscale of the modified version of the Differential Emotions Scale. PANAS-N = Negative Affect subscale of the Positive and Negative Affect Schedule. MASQ-GD = The General Distress subscale of the 30-item version of the Mood and Anxiety Symptom Questionnaire. SAS-SR = Social Adjustment Scale – Self-Report and higher scores indicate poorer social functioning. Two versions of the SOPD group were organized (V1 = version one; V2 = version two) to maximize available data in Step 1. Negative affect group composite score for HC consisted of BDI-IA and DES-N; M-Turk consisted of STAI-S, BDI-IA, DES-N, and PANAS-N; MDD consisted of STAI-S and MASQ-GD; BD consisted of STAI-

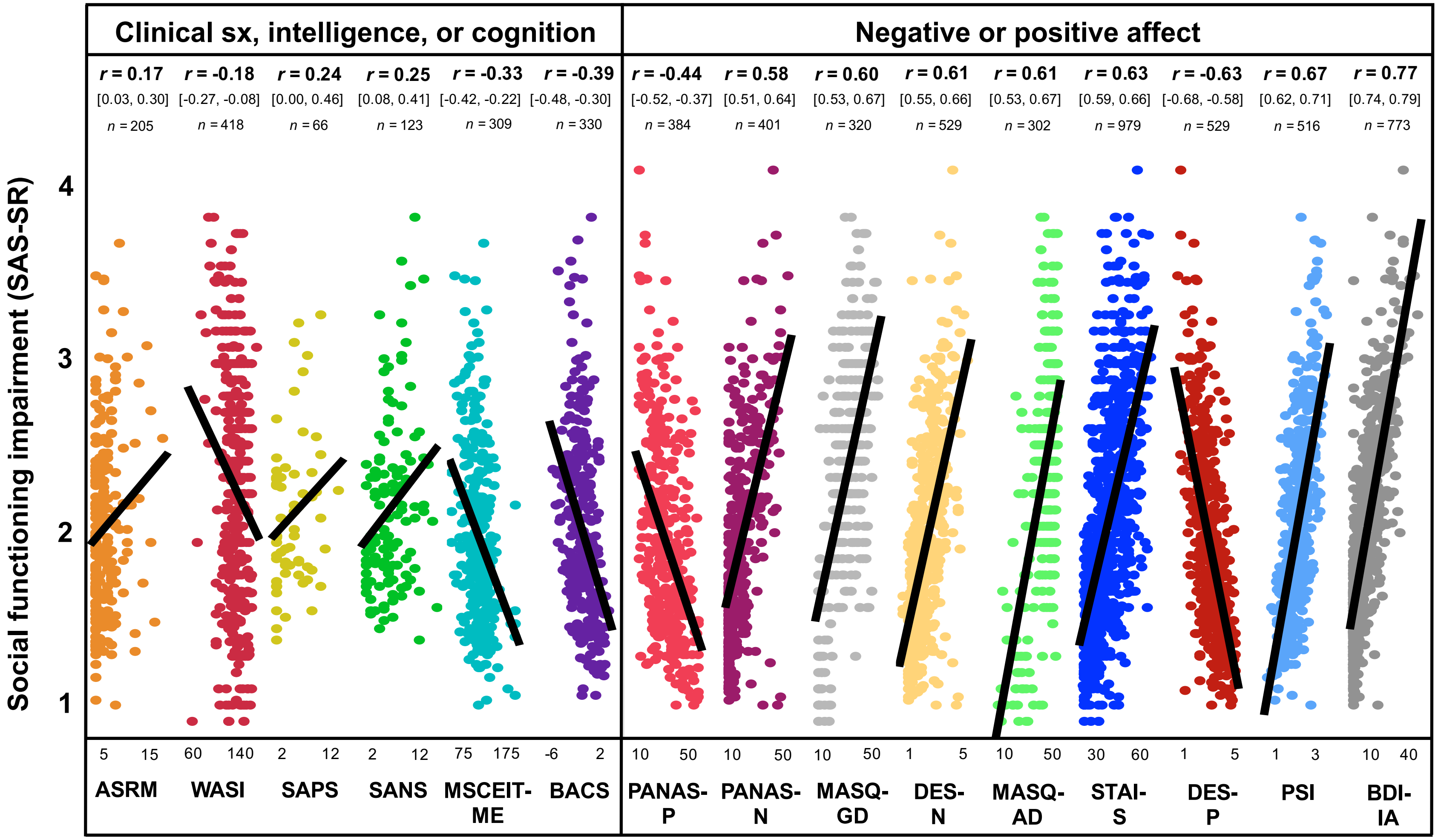
S, BDI-IA, DES-N, PSI, and PANAS-N; SOPD V1 and V2 consisted of BDI-IA and PSI. Positive affect group composite score for HC consisted of DES-P; M-Turk consisted of DES-P and PANAS-P; MDD consisted of MASQ-AD (reverse scored); BD consisted of DES-P and PANAS-P; SOPD V1 had no positive affect group composite score due to a lack of measures; SOPD V2 consisted of DES-P. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 2.1



Note: Correlation between social functioning and negative or positive affect *z*-score for each group. HC = healthy control. M-Turk = Amazon Mechanical Turk. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders. Social functioning impairment indexed by the Social Adjustment Scale – Self-Report (SAS-SR); higher scores indicate social functioning impairment. The composite negative affect or positive affect *z*-score was different for each group. Negative affect composite *z*-score for HC consisted of BDI-IA and DES-N; M-Turk consisted of State-Trait Anxiety Inventory (STAI-S), revised version of the Beck Depression Inventory (BDI-IA), negative subscale of the Differential Emotion Scale (DES-N), and the negative subscale of the Positive and Negative Affect Schedule (PANAS-N); MDD consisted of STAI-S and the General Distress subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-GD); BD consisted of STAI-S, BDI-IA, DES-N, Psychological Stress Index (PSI), and PANAS-N; SOPD consisted of BDI-IA and PSI. Positive affect group composite *z*-score for HC consisted of DES-P; M-Turk consisted of the positive subscale of the Differential Emotion Scale (DES-P) and the positive subscale of the Positive and Negative Affect Schedule (PANAS-P); MDD consisted of the Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AD; reverse scored); BD consisted of DES-P and PANAS-P; SOPD consisted of DES-P. Significant differences between Fisher *r*-to-*z* transformation for all pairwise comparisons are provided above and to the right of each row of graphs.

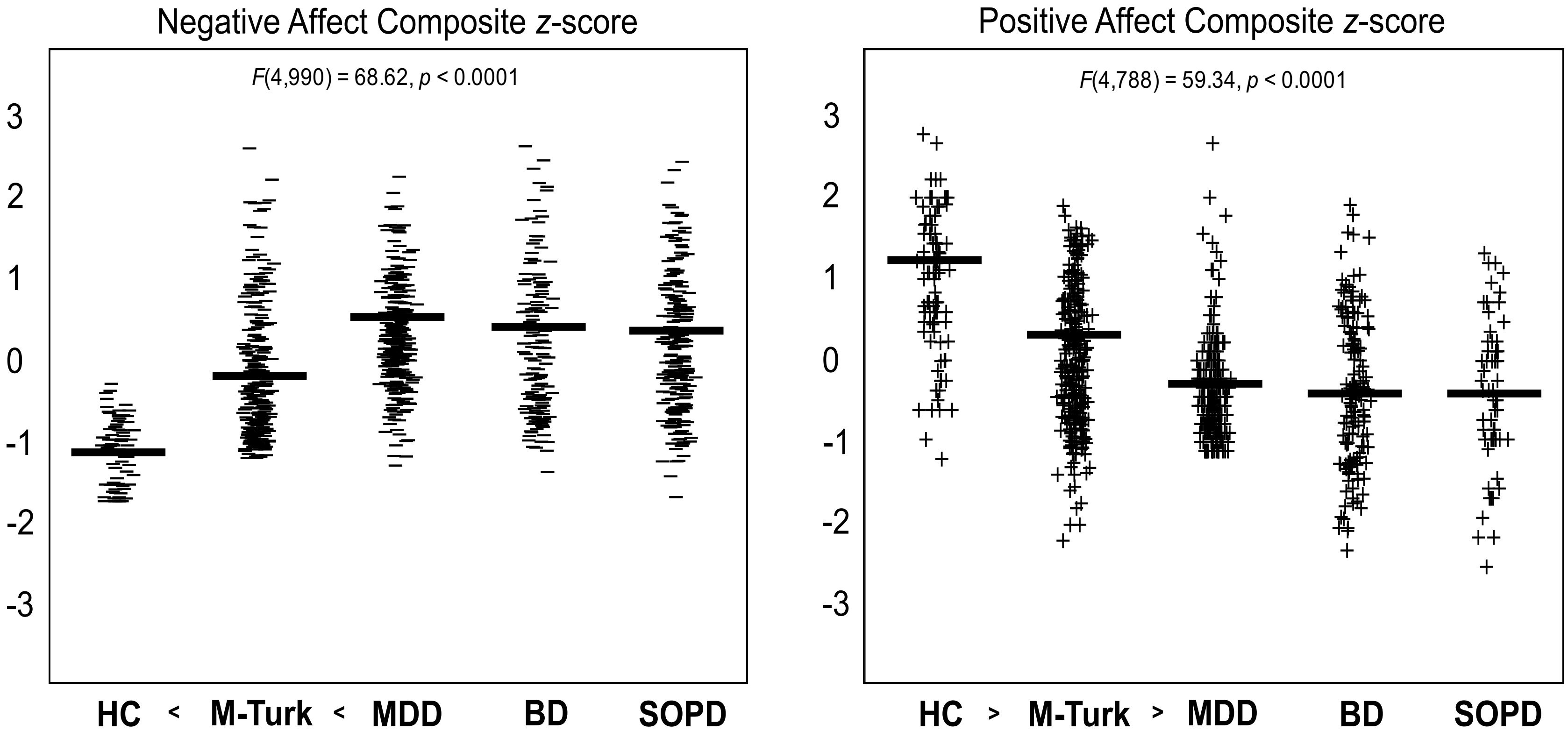
Figure 2.2



Note: Zero-order correlations between social functioning and all clinical variables across all participants. Correlations appear in order from smallest to largest (left to right). All correlations are significant ($p < 0.05$) except for SAPS ($p = 0.051$). ASRM = Altman Self-Rating Mania Scale. WASI =

Wechsler Abbreviated Scale of Intelligence. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. MSCEIT-ME = Managing Emotions branch of the Mayer-Salovey-Caruso Emotional Intelligence Test. BACS = Brief Assessment of Cognition in Schizophrenia. MASQ-GD = General Distress subscale of the Mood and Anxiety Symptom Questionnaire. PANAS-P = Positive affect subscale of the Positive and Negative Affect Schedule. PANAS-N = Negative affect subscale of the Positive and Negative Affect Schedule. DES-N = Negative emotions subscale of the Differential Emotions Scale (modified version). DES-P = Positive emotions subscale of the Differential Emotions Scale (modified version). MASQ-AD = Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire. STAI-S = State anxiety subscale of the State-Trait Anxiety Inventory. PSI = Psychological Stress Index. BDI-IA = Beck Depression Inventory (revised version). SAS-SR = Social Adjustment Scale – Self-Report and higher scores indicate poorer social functioning. Sx = symptoms. The 95% confidence interval is provided in brackets below the effect size of each measure.

Figure 2.3



Note: Group differences in negative and positive affect *z*-score. HC = healthy control. M-Turk = Amazon Mechanical Turk. MDD = Major depressive disorder. BD = Bipolar disorder. SOPD = Schizophrenia and other psychotic disorders. The composite negative affect or positive affect *z*-score was different for each group. Negative affect composite *z*-score for HC consisted of BDI-IA and DES-N; M-Turk consisted of State-Trait Anxiety Inventory (STAI-S), revised version of the Beck Depression Inventory (BDI-IA), negative subscale of the Differential Emotion Scale (DES-N), and the negative subscale of the Positive and Negative Affect Schedule (PANAS-N); MDD consisted of STAI-S and the General Distress subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-GD); BD consisted of STAI-S, BDI-IA, DES-N, Psychological Stress Index (PSI), and PANAS-N; SOPD consisted of BDI-IA and PSI. Positive affect group composite *z*-score for HC consisted of DES-P; M-Turk consisted of the positive subscale of the Differential Emotion Scale (DES-P) and the positive subscale of the Positive and Negative Affect Schedule (PANAS-P); MDD consisted of the Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AD; reverse scored); BD consisted of DES-P and PANAS-P; SOPD consisted of DES-P. Tukey's HSD results are indicated below the x-axis at the group label level; < = significantly less than all the groups to the right; no symbol between group labels indicates no significant group differences.

Supplemental Table 2.1: Psychotropic medications within DSM-IV diagnostic groups

	MDD (*n*=279)	BD (*n*=195)	SOPD (*n*=245)	*t* (df) or χ^2
Daily CPZ equivalents in milligrams (SD)	--	438.0.4 (682.9)	968.5 (4292.4)	1.28
Antipsychotics	--	93 (47.7%)	232 (94.7%)	124.25***
Mood stabilizers	--	121 (62.1%)	67 (27.3%)	53.44***
Antidepressants	133 (48.7%)	104 (53.3%)	110 (44.9%)	3.09
Anxiolytics	--	41 (21.0%)	49 (20.0%)	0.07

Note. CPZ = chlorpromazine. χ^2 = Pearson chi-square. DSM-IV = Diagnostic and Statistical Manual on Mental Disorders – Fourth Edition. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders. Only antidepressant medication data were available for MDD and these data were not available for six MDD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplemental Table 2.2: Pearson correlations between measures of negative/positive affect, neurocognition, general intelligence, social cognition, positive symptoms, negative symptoms, and mania among all participants

	1. DES-P	2. MASQ-AD	3. PANAS-P	4. STAI-S	5. BDI-IA	6. DES-N	7. PSI	8. PANAS-N	9. MASQ-GD
3. PANAS-P	0.69*** (*n*=400)	--							
4. STAI-S	-0.63*** (*n*=521)	0.61*** (*n*=301)	-0.48*** (*n*=400)						
5. BDI-IA	-0.57*** (*n*=510)	--	-0.36*** (*n*=401)	0.73*** (*n*=639)					
6. DES-N	-0.41*** (*n*=529)	--	-0.20*** (*n*=400)	0.70*** (*n*=521)	0.71*** (*n*=510)				
7. PSI	-0.67*** (*n*=253)	--	-0.53*** (*n*=143)	0.67*** (*n*=383)	0.70*** (*n*=515)	0.69*** (*n*=253)			
8. PANAS-N	-0.38*** (*n*=400)	--	-0.17*** (*n*=401)	0.76*** (*n*=400)	0.72*** (*n*=401)	0.75*** (*n*=400)	0.66*** (*n*=143)		
9. MASQ-GD	--	0.67*** (*n*=302)	--	0.60*** (*n*=319)	--	--	--		
10. BACS	0.29** (*n*=126)	--	--	-0.43*** (*n*=205)	-0.34*** (*n*=309)	-0.32*** (*n*=126)	-0.32*** (*n*=309)	--	--
11. WASI	0.10 (*n*=139)	-0.01 (*n*=260)	-0.01 (*n*=139)	-0.12* (*n*=416)	-0.30*** (*n*=139)	-0.28*** (*n*=139)	-0.11 (*n*=138)	-0.32*** (*n*=139)	-0.01 (*n*=277)
12. MSCEIT ME	0.25*** (*n*=248)	--	0.31*** (*n*=144)	-0.32*** (*n*=294)	-0.30*** (*n*=308)	-0.22*** (*n*=248)	-0.27*** (*n*=308)	-0.21* (*n*=144)	--
13. SAPS	-0.15 (*n*=66)	--	--	0.26* (*n*=65)	0.34** (*n*=66)	0.27* (*n*=66)	0.16 (*n*=66)	--	--
14. SANS	-0.21 (*n*=76)	--	--	0.22* (*n*=121)	0.20* (*n*=113)	0.19 (*n*=76)	-0.01 (*n*=113)	--	--
15. ASRM	0.18* (*n*=159)	--	0.32*** (*n*=144)	0.12 (*n*=204)	0.19** (*n*=204)	0.12 (*n*=159)	0.02 (*n*=204)	0.18* (*n*=144)	--

Note. Measures of negative and positive affect are numbered 1-9. Measures of clinical symptoms, intelligence, and cognition are numbered 10-15. The numbering in the first column on the left begins with PANAS-P instead of MASQ-AD because participants who completed MASQ

did not complete DES and thus there is no correlation to test. MASQ-GD = General Distress subscale of the Mood and Anxiety Symptom Questionnaire. PANAS-P = Positive affect subscale of the Positive and Negative Affect Schedule. PANAS-N = Negative affect subscale of the Positive and Negative Affect Schedule. DES-N = Negative emotions subscale of the Differential Emotions Scale (modified version). DES-P = Positive emotions subscale of the Differential Emotions Scale (modified version). MASQ-AD = Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire. STAI-S = State anxiety subscale of the State-Trait Anxiety Inventory. PSI = Psychological Stress Index. BDI-IA = Beck Depression Inventory (revised version). BACS = Brief Assessment of Cognition in Schizophrenia. WASI = Wechsler Abbreviated Scale of Intelligence. MSCEIT-ME = Mayer-Salovey-Caruso Emotional Intelligence Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. ASRM = Altman Self-Rating Mania Scale.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplemental Table 2.3: Hierarchical regression models of individual measures of negative/positive affect predicting social functioning (SAS-SR) variance within each group

	HC		M-Turk		MDD		BD		SOPD			
	(*n*=40)		(*n*=253)		(*n*=203)		(*n*=134)		V1 (*n*=189)		V2 (*n*=46)	
	Variable	Model	Variable	Model	Variable	Model	Variable	Model	Variable	Model	Variable	Model
	b	*ΔR²*	*b*	*ΔR²*	*b*	*ΔR²*	*b*	*ΔR²*	*b*	*ΔR²*	*b*	*ΔR²*
Step 1												
Level of education	-0.10	0.05	-0.16*	0.03*	0.08	0.06**	-0.19*	0.27***	-0.03	0.04*	-0.09	0.16
Sex	-0.23		-0.03		0.12		0.18*		0.18*		0.18	
BACS	0.02				-0.23**				-0.09		-0.31	
WASI							-0.19*					
MSCEIT-ME							-0.31***				0.28	
SAPS											0.09	
SANS											0.18	
ASRM							0.12					
Step 2 (Model A)												
STAI-S			0.66***	0.43***	0.21**	0.04**	0.66***	0.37***				
Step 2 (Model B)												
BDI-IA	0.61***	0.36***	0.74***	0.55***			0.69***	0.37***	0.70***	0.47***	0.67***	0.32***
Step 2 (Model C)												
DES-N	0.34*	0.09*	0.52***	0.27***			0.60***	0.29***				
Step 2 (Model D)												
PSI							0.60***	0.33***	0.56***	0.30***	0.49**	0.18**
Step 2 (Model E)												
PANAS-N			0.49***	0.24***			0.58***	0.27***				
Step 2 (Model F)												
MASQ-GD					0.34***	0.12***						
Step 1												
Level of education	-0.07	0.01	-0.16*	0.03*	0.08	0.05**	-0.19*	0.24***			-0.05	0.13
BACS	-0.01				-0.24**						-0.31	
WASI							-0.21*					
MSCEIT-ME							-0.26**				0.24	
SAPS											0.12	
SANS											0.17	
ASRM							0.11					
Step 2 (Model A)												
DES-P	-0.51**	0.25**	-0.58***	0.33**			-0.62***	0.32***			-0.50***	0.21***
Step 2 (Model B)												
PANAS-P			-0.40***	0.15***			-0.52***	0.21***				
Step 2 (Model C)												
MASQ-AD					-0.28***	0.08***						

Note. Only standardized betas are reported. HC = healthy control. M-Turk = Amazon Mechanical Turk participants. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders. WASI = Weschler Abbreviated Scale of Intelligence. BACS = Brief Assessment of Cognition in Schizophrenia. MSCEIT-ME = Managing Emotions subscale of the Mayer-Salovey-Caruso Emotional Intelligence Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. ASRM =

Altman Self-Rating Mania Scale. DES-P = positive emotions subscale of the Differential Emotions Scale. MASQ-AD = Anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire (reverse scored). BDI-IA = revised version of the Beck Depression Inventory. PSI = Psychological Stress Index. STAI-S = state subscale of the State-Trait Anxiety Index. DES-N = negative emotion subscale of the modified version of the Differential Emotions Scale. PANAS-N = Negative Affect subscale of the Positive and Negative Affect Schedule. MASQ-GD = The General Distress subscale of the 30-item version of the Mood and Anxiety Symptom Questionnaire. SAS-SR = Social Adjustment Scale – Self-Report and higher scores indicate poorer functioning. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplemental Table 2.4: Effect sizes (*r*) from simple regression models of composite and individual negative/ positive affect measures predicting social functioning impairment (SAS-SR) variance within each group

	HC (*n*=40)	M-Turk (*n*=253)	MDD (*n*=203)	BD (*n*=134)	SOPD	
					V1 (*n*=189)	V2 (*n*=46)
Negative affect composite	0.48***	0.70***	0.34***	0.80***	0.71***	0.66***
Positive affect composite	0.49***	0.55***	0.27***	0.59***	--	0.52***
Negative affect measures						
STAI-S		0.67***	0.22**	0.75***		
BDI-IA	0.63***	0.75***		0.77***	0.71***	0.65***
DES-N	0.34*	0.52***		0.71***		
PSI				0.68***	0.57***	0.69***
PANAS-N		0.49***		0.69***		
MASQ-GD			0.35***			
Positive affect measures						
DES-P	0.49**	0.59***		0.40***		0.52***
PANAS-P		0.41***		0.48***		
MASQ-AD			0.27***			

Note. Only standardized betas are reported. HC = healthy control. M-Turk = Amazon Mechanical Turk participants. MDD = major depressive disorder. BD = bipolar disorder. SOPD = schizophrenia and other psychotic disorders. BDI-IA = revised version of the Beck Depression Inventory. PSI = Psychological Stress Index. STAI-S = state subscale of the State-Trait Anxiety Index. DES-N = negative emotion subscale of the modified version of the Differential Emotions Scale. PANAS-N = Negative Affect subscale of the Positive and Negative Affect Schedule. MASQ-GD = The General Distress subscale of the 30-item version of the Mood and Anxiety Symptom Questionnaire. DES-P = positive emotions subscale of the Differential Emotions Scale. PANAS-P = Positive Affect subscale of the Positive and Negative Affect Schedule. MASQ-AD = Anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire. SAS-SR = Social Adjustment Scale – Self-Report and higher scores indicate poorer social functioning. Two versions of the SOPD group were organized (V1 = version one; V2 = version two) to maximize available data in Step 1. Negative affect group composite score for HC consisted of BDI-IA and DES-N; M-Turk consisted of STAI-S, BDI-IA, DES-N, and PANAS-N; MDD consisted of STAI-S and MASQ-GD; BD consisted of STAI-S, BDI-IA, DES-N, PSI, and PANAS-N; SOPD V1 and V2 consisted of BDI-IA and PSI. Positive affect group composite score for HC consisted of DES-P; M-Turk consisted of DES-P and PANAS-P; MDD consisted of MASQ-AD (reverse scored); BD consisted of DES-P and PANAS-P; SOPD V1 had no positive affect group composite score due to a lack of measures; SOPD V2 consisted of DES-P. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

CHAPTER 3

Study 2. Paranoia and the localization of auditory environmental stimuli in schizophrenia

Abstract

Sound localization aides in the detection of threats in the physical and social environment. In schizophrenia (SZ) – a disorder characterized by paranoid thinking and a bias towards threat (e.g., interpreting emotionally neutral stimuli as threatening) – evidence suggests that sound localization is impaired and may contribute to functional deficits. Yet, the factors that contribute to this deficit beyond general cognitive function are relatively unknown. It is possible that sound localization of environmental stimuli is related to paranoia, as such stimuli may evoke threat and improve localization to detect threats. To determine whether the ability to localize environmental stimuli is a function of paranoia, 20 participants with SZ and 22 healthy controls (HC) performed a sound localization task where environmental stimuli were played by eight speakers on a 360-degree horizontal plane and localized. Participants also completed a self-report measure of paranoia in addition to a brief cognitive assessment. SZ performed significantly worse in localizing auditory stimuli than HC. Heightened paranoia in SZ was associated with reduced sound localization impairment, even after accounting for general cognitive function. These findings suggest that sound localization impairment of environmental stimuli is characteristic of SZ, and that paranoia plays a role in sound localization in SZ.

Introduction

Detecting threats within the physical and social environment is necessary to survival. One such tool used to detect threats in the environment is localization of auditory stimuli. The ability to properly localize sounds involves judgment of sound origin (i.e., direction and distance) using binaural cues (e.g., time and level differences between ears) and monaural cues such as spectral information (e.g., frequency; Slee & Young, 2013) that are processed within the auditory system and primary auditory cortex of the brain (Middlebrooks, 2015). In schizophrenia (SZ) – a chronic mental disorder characterized by excessive or irrational ideas of threat (i.e., paranoia; Freeman, 2007) – sound localization impairment has been observed (Balogh & Leventhal, 1982; Balogh, Schuck, & Leventhal, 1979; Matthews, Todd, Budd, Cooper, & Michie, 2007; Perrin et al., 2010). Previous research has identified a relationship between heightened paranoid thinking and cognitive and sensory processing deficits in SZ (Bentall et al., 2009; van der Gaag, 2006), suggesting that reduced cognition and abnormal sensory processing may contribute to the formation and maintenance of false beliefs (Maher, 2005). For example, SZ who experience sensory abnormalities stemming from primary auditory cortex pathophysiology (e.g., sound localization deficits) and cognitive deficits (e.g., executive function impairment) may be prone to paranoid thinking in the face of threatening events. This may cause SZ to misinterpret the environment (e.g., it sounds as though someone is behind me and ready to attack; Asutay & Vastfjall, 2015; Bach, Neuhoff, Perrig, & Seifritz, 2009; Bertels, Kolinsky, Coucke, & Morais, 2013) and lead to a vicious cycle of heightened paranoia. Inversely, heightened paranoia in SZ may increase attention and orienting response (e.g., increased auditory sensitivity) towards non-salient environmental stimuli (Blair & Martaindale, 2014; DeGangi, 2017; Moritz & Laudan, 2007). Both heightened attention and orienting response could lead to improved sound localization to detect threats, possibly in those with intact cognitive resources. Thus, it is unclear if heightened paranoia would enhance or disrupt localization of environmental sounds, and it may depend on one's cognitive functioning. While sound localization studies of SZ have shown impairments compared with healthy controls (HC), and this deficit is related to impaired cognition (Matthews et al., 2007; Perrin et al., 2010), no studies have examined its relationship with both paranoia and cognition. If deficits in sound localization are observed in SZ, and these deficits are related to both paranoia and cognition, the effectiveness of psychosocial treatments designed to improve auditory system functioning via sound localization training paradigms may be impacted by levels of paranoia and cognitive function.

Despite the potential for natural sounds that occur within a social context (e.g., people talking or laughing) to elicit threat or paranoia, the impact of affective valence and arousal level of stimuli on localization is relatively unknown, as previous studies have required HC and SZ to localize only neutral laboratory stimuli such as tones or single-frequencies (Balogh & Leventhal, 1982; Balogh et al., 1979; Perrin et al., 2010). Further, these studies have used a limited localization range (e.g., only a front horizontal or 180-degree plane) and not a full 360-degree horizontal plane, despite the possibility of real-world threats coming from various locations, including sounds from behind. In particular, there is a phenomenon of front/back ambiguity due to typical localization cues being nearly identical (i.e., time and level differences between the ears can be virtually the same; Middlebrooks, 2015) and this ambiguity, along with localization in general, may be further complicated by one's affective response to environmental stimuli. For instance, studies that have examined auditory processing using affective stimuli have been shown that unpleasant or pleasant stimuli, but not neutral stimuli, may elicit enhanced auditory attention compared with neutral stimuli (Brockelmann et al., 2011), but unpleasant compared with pleasant sounds may also impair spatial attention orientating (Bertels et al., 2013). In addition, identification of unpleasant and pleasant auditory stimuli may be slower compared with neutral auditory stimuli (Kryklywy, Macpherson, Greening, & Mitchell, 2013). Thus, auditory processing in terms of sound localization may not only be impacted by levels of paranoia but also affective processing (i.e., valence and/or arousal) of environmental stimuli.

Yet, no studies have explored the relationship between the localization of affective environmental sounds on a 360-degree horizontal plane and paranoid thinking. Thus, the current study examined sound localization of auditory environmental stimuli that varied by valence, arousal, and location along a 360-degree horizontal plane in SZ and HC. Based on previous findings of impaired sound localization in SZ relative to healthy individuals (Balogh, 1979; Perrin, 2010), we predicted significant group differences in overall sound localization accuracy, with SZ performing worse than HC. We also predicted a relationship between sound localization and paranoia while accounting for general cognition in SZ, with the possibility of heightened paranoia being associated with improved or reduced sound localization performance. Due to the lack of available data in the current literature, we explored if sound localization varied according to valence and/or arousal within or between each group.

Methods

Participants

A total of 20 SZ and 22 HC completed the study. A Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 2000) diagnosis of schizophrenia/schizoaffective disorder or absence of an Axis I diagnosis was established using the Structured Clinical Interview for the DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997). SZ were recruited via a university research registry, mental health clinics, other research studies, and advertisements. SZ who were unable to provide informed consent or had a history of substance dependence/abuse in the past 12 months were excluded. HC with a history of a DSM-IV Axis I diagnosis, significant medical conditions that affect brain functions, or family history of psychosis or mania among first-degree relatives were excluded. All participants were 21-65 years of age with no history of auditory impairment. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and the research protocol was approved by the Institutional Review Board of the University of Michigan Medical School. Written informed consent was obtained from each participant prior to data collection.

Procedure

SZ were first diagnostically and clinically assessed with the SCID-P, SAPS, SANS, and YMRS. HC participants were diagnostically assessed with the SCID-NP. All participants completed a neurocognitive assessment. All diagnostic, clinical, and cognitive assessments were conducted by a clinical psychology doctoral student. All participants then completed self-report measures of mood, anxiety, and paranoia, followed by the sound localization paradigm. Participants also completed a probabilistic reasoning paradigm not reported here.

Auditory stimuli

Forty-eight environmental stimuli from the International Affective Digitized Sounds (IADS; Bradley, 2007) were selected to create three valence categories (pleasant, neutral, and unpleasant) for the sound localization task. Examples of IADS stimuli include a baby crying and a babbling brook. Bradley (2007) used the Self-Assessment Manikin (Bradley & Lang, 1994) to determine both pleasantness (i.e., valence) and excitement (i.e., arousal) on a Likert scale from one to nine. Higher valence or arousal ratings indicate more unpleasantness or excitement, respectively. Based on the valence ratings of Bradley (2007), cut-offs for each category were established and 16 pleasant stimuli (valence cut-off > 5.5; mean valence = 6.8 and mean arousal = 5.2), 16 neutral stimuli (valence cut-off >= 4.5 and <= 5.5; mean valence = 5.0 and mean arousal = 4.8), and 16 unpleasant stimuli (valence cut-off < 4.5; mean valence = 2.6 and mean arousal = 6.6) were selected for the current study. Mean arousal level of the unpleasant stimuli was not matched to neutral or pleasant stimuli due to a lack of IADS unpleasant stimuli that do not elicit higher levels of arousal (e.g., low valence and arousal stimuli are limited to sounds of sexual intercourse). Considering that each IADS stimulus is up to six seconds in duration, and that most localization paradigms use stimuli lasting one second or less (cf. Bednar, Boland, & Lalor, 2017; Lewald, Hanenberg, & Getzmann, 2016), all stimuli were trimmed to one second in duration to ensure that any differences in principle findings of this study and previous studies are not due to differences in stimuli duration. The 48 trimmed stimuli were then confirmed to have valence ratings similar to Bradley (2007) via valence and arousal ratings completed by 11 members of our research lab using the same Self-Assessment Manikin (Bradley & Lang, 1994) rating scale as Bradley (2007). These ratings are referred to as the standardized valence and arousal ratings in the rest of this report, with the pleasant sounds having a mean valence rating of 6.4 (mean arousal = 4.9), neutral sounds a mean valence of 5.1 (mean arousal = 4.7), and unpleasant sounds a mean valence of 2.6 (mean arousal = 6.4).

Valence/Arousal ratings

Participants were placed in a seat in the center of a circle located within the sound localization room. Prior to performing the sound localization task, they first listened to the 48 sound stimuli with headphones and rated each for valence and arousal using a Likert scale from one to nine on a Mac computer running MATLAB software (Mathworks, Inc.). Lower values for valence and arousal indicated pleasant valence or lower arousal, respectively.

Sound localization task

After completing the valence/arousal ratings, participants remained seated in the center of the circle with a radius of 3 feet. A circular apparatus standing three feet tall was lined with 16 evenly distributed speakers along the circumference (Figure 1). Eight of the speakers (placed at 45, 90, 135, 180, 225, 270, 315, and 360 degrees) were active and the other eight were inactive decoy speakers (placed at 22.5, 67.5, 112.5, 147.5, 202.5, 247.5, 292.5, and 337.5 degrees). The 48 sounds were presented, one at a time, in a pseudorandom order from one of the eight active speakers, such that each speaker presented six sounds in total. Each sound was presented at approximately 60 decibels or the level of normal conversation. Participants were instructed to identify the location of each sound by clicking on a spot along the circumference of a circle representing the speaker configuration on the screen of a Mac computer placed in front of them (Figure 1). Speakers were not identified or represented on this circle, and participants could click anywhere on this circle, allowing for the measurement of sound localization as a continuous variable. A chinrest was used to keep participants' head centered in relation to the speakers. All stimuli were presented using a Mac computer running MATLAB software (Figure 1). Immediately before the sound localization task, eight different IADS stimuli were localized during a practice session to reduce learning effects.

Self-report questionnaires

All participants completed the Green et al. Paranoid Thoughts Scale (GPTS; Green et al., 2008), which includes subscale assessments of Ideas of Reference and Persecution. Levels of depression and anxiety were assessed with the revised version of the Beck Depression Inventory (BDI-IA; Beck & Steer, 1993) and the state subscale of the State-Trait Anxiety Inventory (STAI-S; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), respectively.

Cognitive and clinical assessment

Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe, 1999), which includes domains of working memory, processing speed, and executive function. Within SZ only, overall positive symptoms were assessed with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b), and a detailed assessment of auditory hallucinations was performed with the Auditory Hallucinations Rating Scale (AHRS; Haddock, 1994). Also in SZ only, negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a).

Data Analyses

Demographic and clinical characteristics of the groups were compared with chi-square or simple *t*-test (Table 1).

Valence and arousal ratings over the 48 stimuli were computed for each participant. To determine group differences in valence/arousal ratings, mean valence and arousal ratings of the three categories (i.e., pleasant, neutral, and unpleasant) were compared between SZ and HC using simple *t*-tests. Using the previous cut-offs for valence categories (pleasant > 5.5; neutral between 4.5 and 5.5; and unpleasant < 4.5), both groups rated IADS stimuli similar to Bradley (2007) and our research lab: HC pleasant mean = 7.0 (arousal mean = 4.0), neutral mean = 5.0 (arousal mean = 3.7), and unpleasant mean = 2.6 (arousal mean = 5.7); SZ pleasant mean = 7.3 (arousal mean = 4.3), neutral mean = 5.0 (arousal mean = 4.4), and unpleasant mean = 2.5 (arousal mean = 6.0). HC rated 40.9% of stimuli as pleasant, 25.9% neutral, and 33.2% unpleasant. SZ rated 41.4% of stimuli as pleasant, 18.9% neutral, and 39.7% unpleasant. To determine group differences in valence/arousal ratings, mean valence and arousal ratings of the three categories (i.e., pleasant, neutral, and unpleasant) were compared between SZ and HC using simple *t*-tests. Mean valence ratings for pleasant, neutral, and unpleasant sounds were not significantly different between HC and SZ (*p*'s > 0.05). Mean arousal ratings for each of the three valence categories were also not significantly different between HC and SZ (*p*'s > 0.05). Mean valence and arousal ratings were not significantly different between HC and SZ, *t*(40) = -0.28, *p* = 0.784, and *t*(40) = 1.33, *p* = 0.192, respectively, even after removing one HC outlier for valence (3 standard deviations above the group mean; Supplemental Figure 1). Supplemental Figure 2 provides a scatterplot of each IADS stimuli mapped onto valence and arousal, along with a scatterplot of IADS stimuli with a mean rating difference of one or more for valence and/or arousal.

Sound localization performance was measured by absolute error— click distance in degrees from the correct speaker. Although click distance to that was counter-clockwise to the correct speaker was recorded as negative and clockwise positive, absolute value allows for proper assessment of performance, as raw error includes both negative and positive values and could cancel out error across trials. For example, the addition of a -45-degree and a 45-degree error would equal zero, which is an incorrect representation of the performance. Thus, deviation from either direction (click distance left or right of the correct speaker) is coded the same. The range of absolute error was 0 to 180 degrees for each trial.

Since sound localization on a 360-degree horizontal plane can result in front/back ambiguity due to the lack of time and intensity cues (e.g., sounds from the back are thought to come from the front), the number of these “reversals” was counted (i.e., all errors over 90 degrees were counted) for each participant. Because of the use of absolute values, along with a high propensity to accurately localize sounds but also experience “reversals”, performance data of individual trials approximate a gamma distribution (i.e., all values are non-negative values with high concentration near zero and a long right tail). Generalized linear mixed models (GLM) were used to determine if group differences in absolute error at the individual trial level varied by valence/arousal. These models have the option to select the distribution of the dependent variable, which in this case is a gamma distribution based on visual inspection of a histogram and confirmed by comparing the information criterion (i.e., AIC and BIC) of models with a normal versus gamma distribution. A value of one was artificially added to each absolute error value, as GLM using SPSS software with a gamma distribution requires non-zero values (IBM, 2018). In all cases, GLM with a gamma distribution had the winning information criteria over GLM with a normal distribution, confirming that the data is best modeled as a gamma distribution. In the first GLM, group (HC or SZ) and individual participant ratings of valence and arousal were entered as fixed effects predicting sound localization absolute error. In the second GLM, group and standardized ratings of valence and arousal as determined by Bradley (2007) and confirmed by our 11 lab members were entered as fixed effects predicting sound localization error. GLM were run with main effects, and all possible interactions of main effects were entered individually. Only significant interactions were included in the final winning model, which was selected based on the model information criteria (i.e., AIC and BIC).

To explore for group differences in front/back ambiguity, a simple *t*-test was used to compare the frequency of reversals between SZ and HC.

Pearson and Spearman’s rank-order correlation analysis was used to examine the relationship between mean absolute error in the localization task and GPTS and BACS, along with clinical assessments (SAPS and AHRS) in SZ. Partial correlation analysis was used to explore the relationship between mean absolute error and GPTS while controlling for BACS in SZ.

Results

Sound localization

The results of GLM showed that sound localization performance was significantly worse in SZ compared with HC. The results of GLM also showed that there were no sound localization differences according to individual valence and/or arousal ratings of stimuli across participants. However, there were sound localization differences among stimuli according to standardized valence and arousal ratings, along with an interaction between these valence and arousal ratings (Table 2). Specifically, reduced valence and arousal were associated with better localization performance. An interaction plot was created to illustrate the valence/arousal interaction by artificially separating valence into pleasant, neutral, and unpleasant categories using the previous cut-offs (pleasant > 5.5; neutral between 4.5 and 5.5; and unpleasant < 4.5) and preserving arousal as a continuous variable (Figure 4). Beta estimate suggested that each one unit increase of valence results in a 1.03 unit of decrease in the relationship between arousal and absolute error. That is, the effect of arousal on absolute error increases as valence becomes more unpleasant across participants.

There was a significant negative correlation between mean absolute error and GPTS in SZ but not HC (top of Figure 2). There was no significant correlation between mean absolute error and BACS in SZ or HC (bottom of Figure 2). Partial correlation analysis showed that the relationship between mean absolute error and GPTS in SZ remained significant after controlling for BACS (Figure 3). Among SZ, there were no significant correlations between mean absolute error and SAPS, $r(20) = -0.30$, $p = 0.195$ and $r_s(20) = -0.29$, $p = 0.22$; or AHRS, $r(20) = 0.16$, $p = 0.493$, and $r_s(20) = 0.10$, $p = 0.674$.

As expected, for both groups the distribution of error showed “reversals” where sounds originating from the back speaker were incorrectly localized as coming from the front speaker (i.e., ~180 degrees away). The percentage of reversals was significantly higher in SZ (9.0%) compared with HC (5.7%), $t(40) = 2.23$, $p = 0.032$.

Discussion

The current study examined the localization of auditory environmental stimuli and the relationship between sound localization and paranoia in people with schizophrenia and those with no history of mental illness. It was found that SZ performed significantly worse during a sound localization paradigm than HC. Levels of paranoia were associated with sound localization deficits in SZ, such that the greatest sound localization deficits were observed in those with reduced levels of paranoia. SZ with heightened paranoia had the highest sound localization accuracy, even after accounting for cognitive function. Considering that there were no differences in localization according to individual ratings of valence and/or arousal of environmental stimuli for both groups, it’s possible that SZ with higher levels of paranoia experience an attentional bias to threat that enhances localization of sounds regardless of the valence/arousal elicited by stimuli, as more cognitive resources may be allocated towards possible or perceived threats. Specifically, enhanced auditory processing via an involuntary orienting response that is triggered by changes in the environment and ensures optimal perception of stimuli (Blair & Martaindale, 2014; DeGangi, 2017) and involuntary attention towards stimuli in conditions that evoke threat (Dominguez-Borras, Rieger, Corradi-Dell'Acqua, Neveu, & Vuilleumier, 2017; Lv, Wang, Tu, Zheng, & Qiu, 2011) may accompany heightened paranoia and cognitive processing of both threatening and non-salient stimuli in SZ (Freeman, 2007).

Further, sound localization impairment in SZ was in part driven by front-to-back ambiguity resulting in ‘reversals’ where sounds from the front were incorrectly localized as coming from the back. While SZ made significantly more of these errors than HC, both groups experienced reversals, and this may have been caused by indistinguishable localization cues for sounds coming from the front or back. Sound intensity and time differences between the ears are almost identical for sounds coming from the front or back. In these situations, localizers must rely more heavily on spectral features of stimuli (i.e., a range in the intensity of frequencies) that are detected by the direction-dependent filtering effects of the head and ears. All of these cues must be integrated and assigned salience. Moreover, looking towards the source of auditory stimuli improves localization (Keating & King, 2015; Middlebrooks, 2015), which participants in the current study were not able to do during stimuli presented from the back (or sides). All of these factors (i.e., sound intensity, time difference between the ears, and fixed head position) may explain why sounds coming from the front were not ‘reversed’ nearly as often as sounds coming from the back. Considering the relationship between heightened paranoia and improved overall localization in SZ, along with reversals contributing to absolute error, it is possible that increased sensory resources that come with threat and salience (e.g., orienting response) aid in the detection of spectral cues, which may help to reduce reversals in SZ with heightened paranoia. In addition, prior experience and behavioral goals are unexplored areas of sound localization that may contribute to performance (Keating & King, 2015). Heightened paranoia may provide further motivation to interpret the environment, resulting in a larger allocation of sensory/cognitive resources.

Finally, the causal relationship between sound localization and paranoia in SZ is currently unknown. Previous findings of abnormal sensory experiences leading to paranoia (e.g., heightened paranoia has been reported in older adults with hearing loss; Freeman, 2007), suggest a cascading effect of sensory abnormalities leading to heightened paranoia. However, the current findings do not support this cascading effect, rather, heightened paranoia may enhance attention and orienting response localization despite sound localization deficits in SZ relative to HC. Induction studies could help determine the causal relationship between localization and paranoia in clinical groups. If localization performance was worse in the neutral induction group compared with the paranoia induction group, it would suggest that heightened paranoia positively impacts sound localization.

To our knowledge, this is first study to examine sound localization of environmental stimuli in SZ. Previous studies have examined localization of tones or single frequencies rather than more spectrally complex stimuli that occur naturally in the environment and found localization deficits in SZ were related to a pattern of localization impairment in both right and left hemifields similar to those with right superior temporal lobe lesions that include the primary auditory cortex (Perrin et al., 2010). Previous reports have identified sound lateralization abnormalities due to interaural processing impairment of time and phase but not other spatial information such as loudness, which suggest localization impairment maybe driven by impaired processing of temporal interaural cues. This selective deficit lends itself to the current findings, as temporal cues help to localize stimuli in more complex environments and thus natural settings that include both high and low frequency auditory information. Neural firing abnormalities in the auditory system and precuneus may explain temporal interaural deficits (Matthews et al., 2007; Zundorf, Lewald, & Karnath, 2013). Taken together, these findings suggest that the sound localization impairment observed in the current study may be related to impairment of the primary auditory cortex and auditory system in SZ. While the current study found no relationship between overall cognitive function (i.e., working memory, processing speed, and executive function) and sound localization, more specific assessment of the auditory system and related regions necessary for both auditory processing and sensory integration may be needed. Further, since the current study examines only behavioral data, biological abnormalities can only be speculated, and future studies are needed to explore this hypothesis using psychophysiological techniques (e.g., event related potential) during sound localization paradigms. Further, improving functioning of the auditory system in SZ via existing sound localization training paradigms may lead to reduced sound localization impairment and functioning, although heightened paranoia status may impact training effectiveness (i.e., SZ with reduced levels of paranoia may experience the greatest localization gains from such training paradigms).

The current study found differences in sound localization according to standardized but not individual ratings of valence and/or arousal for both SZ and HC. For sounds with standardized ratings of valence/arousal, better localization performance was related to more unpleasant or less arousing sounds, along with an increased effect of arousal on performance with more unpleasant sounds. Previous reports suggest that auditory processing differences in unpleasant or pleasant compared with neutral standardized stimuli may be explained by enhanced auditory attention (Bertels et al., 2013; Brockelmann et al., 2011; Kryklywy et al., 2013). Within the current study, the pattern of performance for both groups may indicate enhanced auditory attention to sounds that are both unpleasant and less arousing (e.g., someone saying “ouch” after a non-severe injury). Yet for individual ratings of valence and arousal, the previous pattern was not found, and the lack of differences in sound localization according to valence/arousal suggest that attention is enhanced towards all stimuli, rather than stimuli that may be perceived as threatening due to the elicited valence or arousal of the stimuli (especially for SZ with heightened paranoia). Previous research has also found support for this hypothesis, as a threat bias may generalize to all stimuli depending on the context (Dominguez Mde, Viechtbauer, Simons, van Os, & Krabbendam, 2009). Sensory resources and salience may be assigned to benign or irrelevant stimuli that is perceived as threatening via the orienting response, which would support aberrant salience models of psychosis (Lau, Wang, Hsu, & Liu, 2013). While there are no studies that have compared standardized categories of valence/arousal with individual ratings in SZ and HC, the current findings also suggest that standardized ratings may have limited generalizability to both clinical populations and those with no history of mental illness (e.g., IADS ratings are based on a college population).

The current sound localization paradigm was limited by the use of an echoic room. However, sound absorbing material was placed in the corners of the localization room to reduce echoes. Speakers were also calibrated periodically to ensure speaker volumes were approximately 60 decibels. Stimuli were randomly played for each participant, meaning no pattern of sounds was the same, thereby eliminating the probability of a speaker location or specific speaker leading to the current findings. However, differences in spectral composition of single-frequency auditory stimuli versus the complexity of auditory environmental stimuli also complicate the interpretation of the current findings. It is also possible that the IADS stimuli used in the current study, which were categorized by valence and not balanced for arousal, impacted the results. Less arousing sounds were typically more pleasant and more arousing sounds were typically more unpleasant, and arousal levels for pleasant and neutral did not match the arousal level for unpleasant sounds, creating a possible confound. It is possible that the observed the effect of standardized arousal on sound localization error would not exist if unpleasant but low arousal sounds were used. Replication of the current findings with stimuli balanced for both valence and arousal using a larger sample size is needed.

The findings of the current study suggest that impaired localization of environmental sounds is characteristic of schizophrenia compared with healthy controls. Within SZ, it was found that lower levels of paranoia were associated with sound localization impairment while higher levels of paranoia were associated with improved sound localization, even after accounting for cognitive function. It is possible that heightened paranoia may lead to a shift in cognitive resources towards threat detection via localization of environmental sounds regardless of valence/arousal.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Andreasen, N. C. (1984a). *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa.

Andreasen, N. C. (1984b). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa.

Asutay, E., & Vastfjall, D. (2015). Attentional and emotional prioritization of the sounds occurring outside the visual field. *Emotion, 15*(3), 281-286. doi:10.1037/emo0000045

Bach, D. R., Neuhoff, J. G., Perrig, W., & Seifritz, E. (2009). Looming sounds as warning signals: the function of motion cues. *International Journal of Psychophysiology, 74*(1), 28-33. doi:10.1016/j.ijpsycho.2009.06.004

Balogh, D. W., & Leventhal, D. B. (1982). The use of temporal and amplitude cues by schizophrenics, psychiatric controls, and aged normals in auditory lateralization. *J Nerv Ment Dis, 170*(9), 553-560.

Balogh, D. W., Schuck, J. R., & Leventhal, D. B. (1979). A study of schizophrenics' ability to localize the source of a sound. *J Nerv Ment Dis, 167*(8), 484-487.

Beck, A. T., & Steer, R. A. (1993). *Manual for the Beck Depression Inventory*. San Antonio, TX: Psychological Corporation.

Bednar, A., Boland, F. M., & Lalor, E. C. (2017). Different spatio-temporal electroencephalography features drive the successful decoding of binaural and monaural cues for sound localization. *Eur J Neurosci, 45*(5), 679-689. doi:10.1111/ejn.13524

Bentall, R. P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., . . . Corcoran, R. (2009). The cognitive and affective structure of paranoid delusions: a transdiagnostic investigation of patients with schizophrenia spectrum disorders and depression. *Arch Gen Psychiatry, 66*(3), 236-247. doi:10.1001/archgenpsychiatry.2009.1

Bertels, J., Kolinsky, R., Coucke, D., & Morais, J. (2013). When a bang makes you run away: spatial avoidance of threatening environmental sounds. *Neurosci Lett, 535*, 78-83. doi:10.1016/j.neulet.2012.12.058

Blair, J. P., & Martaindale, M. H. (2014). *Evaluating Police Tactics: An Empircal Assessment of Room Entry Techniques*: Routledge.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *J Behav Ther Exp Psychiatry, 25*(1), 49-59.

Bradley, M. M., Lang, Peter J. (2007). *The International Affective Digitized Sounds (2nd Edition; IADS-2): Affective Ratings of Sounds and Instruction Manual*. Technical report B-3. University of Florida, Gainesville, FL.

Brockelmann, A. K., Steinberg, C., Elling, L., Zwanzger, P., Pantev, C., & Junghofer, M. (2011). Emotion-associated tones attract enhanced attention at early auditory processing: magnetoencephalographic correlates. *J Neurosci, 31*(21), 7801-7810. doi:10.1523/JNEUROSCI.6236-10.2011

DeGangi, G. (2017). *Pediatric Disorders of Regulation in Affect and Behavior: A Therapist's Guide to Assessment and Treatment* (2nd ed.): Academic Press.

Dominguez Mde, G., Viechtbauer, W., Simons, C. J., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychol Bull, 135*(1), 157-171. doi:10.1037/a0014415

Dominguez-Borras, J., Rieger, S. W., Corradi-Dell'Acqua, C., Neveu, R., & Vuilleumier, P. (2017). Fear Spreading Across Senses: Visual Emotional Events Alter Cortical Responses to Touch, Audition, and Vision. *Cereb Cortex, 27*(1), 68-82. doi:10.1093/cercor/bhw337

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version, Administration Booklet*: American Psychiatric Press.

Freeman, D. (2007). Suspicious minds: the psychology of persecutory delusions. *Clin Psychol Rev, 27*(4), 425-457. doi:10.1016/j.cpr.2006.10.004

Green, C. E., Freeman, D., Kuipers, E., Bebbington, P., Fowler, D., Dunn, G., & Garety, P. A. (2008). Measuring ideas of persecution and social reference: the Green et al. Paranoid Thought Scales (GPTS). *Psychol Med, 38*(1), 101-111. doi:10.1017/S0033291707001638

Haddock, G. (1994). *Auditory Hallucinations Rating Scale*. University of Manchester.

IBM. (2018). Generalized linear models. *Knowledge Center.* Retrieved from https://www.ibm.com/support/knowledgecenter/en/SSLVMB_22.0.0/com.ibm.spss.statistics.help/spss/advanced/idh_idd_genlin_typeofmodel.htm

Keating, P., & King, A. J. (2015). Sound localization in a changing world. *Curr Opin Neurobiol, 35*, 35-43. doi:10.1016/j.conb.2015.06.005

Keefe, R. (1999) Brief Assessment of Cognition in Schizophrenia (BACS). Duke University Medical Center.

Kryklywy, J. H., Macpherson, E. A., Greening, S. G., & Mitchell, D. G. (2013). Emotion modulates activity in the 'what' but not 'where' auditory processing pathway. *Neuroimage, 82*, 295-305. doi:10.1016/j.neuroimage.2013.05.051

Lau, C. I., Wang, H. C., Hsu, J. L., & Liu, M. E. (2013). Does the dopamine hypothesis explain schizophrenia? *Rev Neurosci, 24*(4), 389-400. doi:10.1515/revneuro-2013-0011

Lewald, J., Hanenberg, C., & Getzmann, S. (2016). Brain correlates of the orientation of auditory spatial attention onto speaker location in a "cocktail-party" situation. *Psychophysiology, 53*(10), 1484-1495. doi:10.1111/psyp.12692

Lv, J. Y., Wang, T., Tu, S., Zheng, F., & Qiu, J. (2011). The effect of different negative emotional context on involuntary attention: an ERP study. *Brain Res Bull, 86*(1-2), 106-109. doi:10.1016/j.brainresbull.2011.06.010

Maher, B. (2005). Delusional thinking and cognitive disorder. *Integr Physiol Behav Sci, 40*(3), 136-146.

Matthews, N., Todd, J., Budd, T. W., Cooper, G., & Michie, P. T. (2007). Auditory lateralization in schizophrenia--mismatch negativity and behavioral evidence of a selective impairment in encoding interaural time cues. *Clin Neurophysiol, 118*(4), 833-844. doi:10.1016/j.clinph.2006.11.017

Middlebrooks, J. C. (2015). Sound localization. *Handb Clin Neurol, 129*, 99-116. doi:10.1016/B978-0-444-62630-1.00006-8

Moritz, S., & Laudan, A. (2007). Attention bias for paranoia-relevant visual stimuli in schizophrenia. *Cogn Neuropsychiatry, 12*(5), 381-390. doi:10.1080/13546800601119982

Perrin, M. A., Butler, P. D., DiCostanzo, J., Forchelli, G., Silipo, G., & Javitt, D. C. (2010). Spatial localization deficits and auditory cortical dysfunction in schizophrenia. *Schizophr Res, 124*(1-3), 161-168. doi:10.1016/j.schres.2010.06.004

Slee, S. J., & Young, E. D. (2013). Linear processing of interaural level difference underlies spatial tuning in the nucleus of the brachium of the inferior colliculus. *J Neurosci, 33*(9), 3891-3904. doi:10.1523/JNEUROSCI.3437-12.2013

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

van der Gaag, M. (2006). A neuropsychiatric model of biological and psychological processes in the remission of delusions and auditory hallucinations. *Schizophr Bull, 32 Suppl 1*, S113-122. doi:10.1093/schbul/sbl027

Zundorf, I. C., Lewald, J., & Karnath, H. O. (2013). Neural correlates of sound localization in complex acoustic environments. *PLoS One, 8*(5), e64259. doi:10.1371/journal.pone.0064259

Acknowledgements

The authors declare no conflicts of interests. The study was funded by Blue Cross Blue Shield of Michigan (grant number 2105.SAP to TBG) and Rackham Graduate School at the University of Michigan (student grant to TBG).

Table 3.1: Demographic and baseline clinical measures for all participants

	HC (*n*=22)	SZ (*n*=20)	*t*/Chi-square/ FET[a]
Age in years (SD)	42.9 (14.8)	40.8 (13.0)	-0.66
Sex (Male/Female)	12/10	10/10	0.09
Years of education	16.7 (2.3)	15.0 (1.9)	-2.75**
Race (White/Other)	16/6	13/7	0.29
Handedness (Right/Left)	22/0	17/3	0.10
BACS	0.0 (1.0)	-0.55 (0.75)	-2.02*
BDI-IA	0.8 (1.6)	8.6 (6.6)	5.37***
STAI-S	26.5 (4.1)	36.9 (9.6)	4.83***
GPTS	34.5 (4.6)	56.3 (27.1)	3.96***
SCID-IV diagnosis (SZ/SA)		9/11	
Number of hospitalizations		4.4 (3.3)	
Duration of illness (years)		15.2 (7.0)	
SAPS		5.1 (3.6)	
SANS		5.6 (3.1)	
AHRS		12.8 (12.4)	

Note: FET = Fisher's Exact Test and the statistic provided is table probability. BACS = Brief Assessment of Cognition in Schizophrenia composite *z*-score. BDI-IA = revised version of the Beck Depression Inventory. STAI-S = state subscale of the State-Trait Anxiety Inventory. GPTS = Green et al. Paranoid Thoughts Scale. SCID-IV = Structured Clinical Interview for the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders. SZ = schizophrenia. SA = schizoaffective. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. AHRS = Auditory Hallucination Rating Scale.

Table 3.2: Summary of final generalized linear mixed models for sound localization via absolute error by group, valence, and arousal

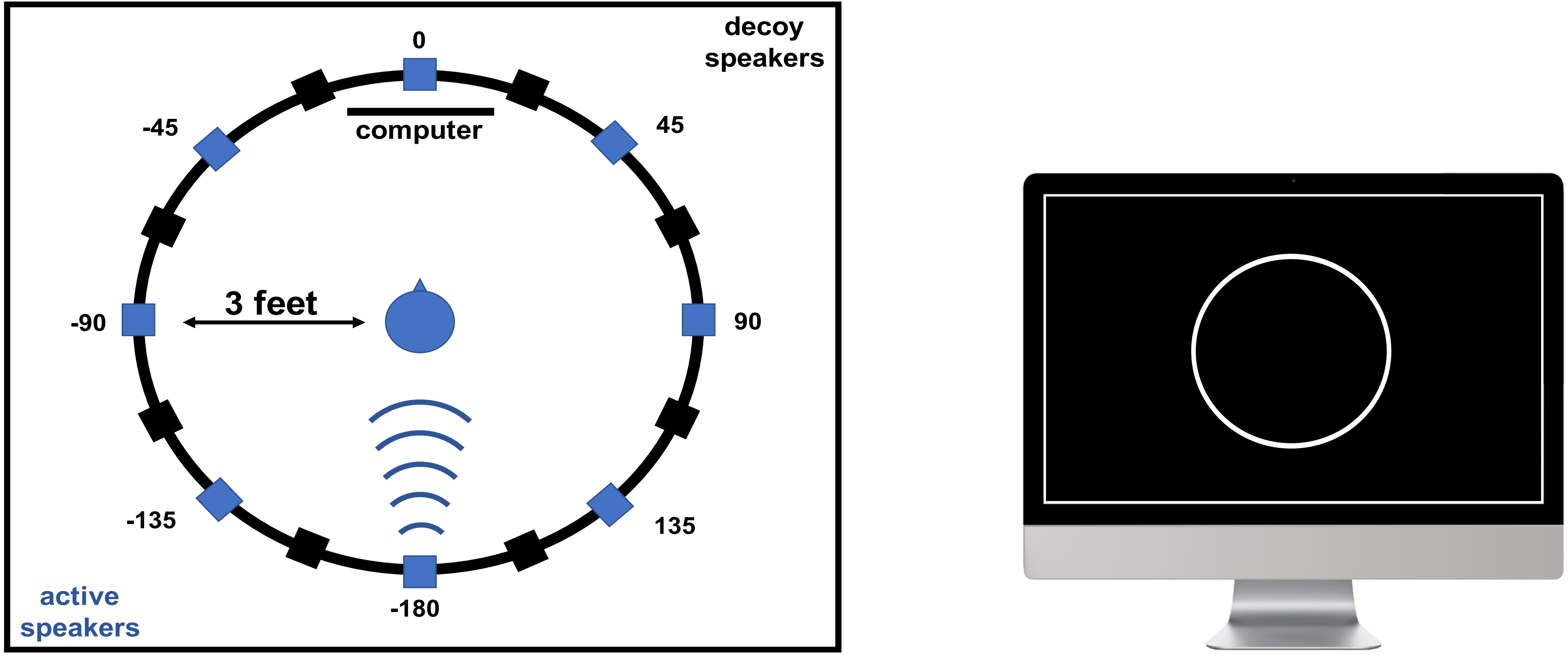
	Individual valence/arousal	Standardized valence/arousal
	Absolute error[a]	Absolute error[a]
Tests for Model Effects (Wald Chi-Square)		
Intercept	84.9***	0.81
Group (HC or SZ)	32.21***	27.05***
Valence	0.60	7.83**
Arousal	0.58	8.28**
Valence*Arousal	--	6.74**
Parameter Estimates[b]	*β (s.e.)*	*β (s.e.)*
Intercept	31.31 (3.19)***	-7.15 (11.95)
Group (HC)	-8.07 (1.42)***	-7.14 (1.37)***
Valence	-0.26 (0.34)	6.66 (2.38)**
Arousal	-0.25 (0.33)	5.41 (1.88)**
Valence*Arousal	--	-1.03 (0.40)**
Model Information Criteria		
Akaike	15991.15	16645.29
Bayesian	16018.99	16678.94

a. Each absolute error value has been increased by one to avoid convergence errors within each generalized linear mixed model.

b. Redundant parameters omitted.

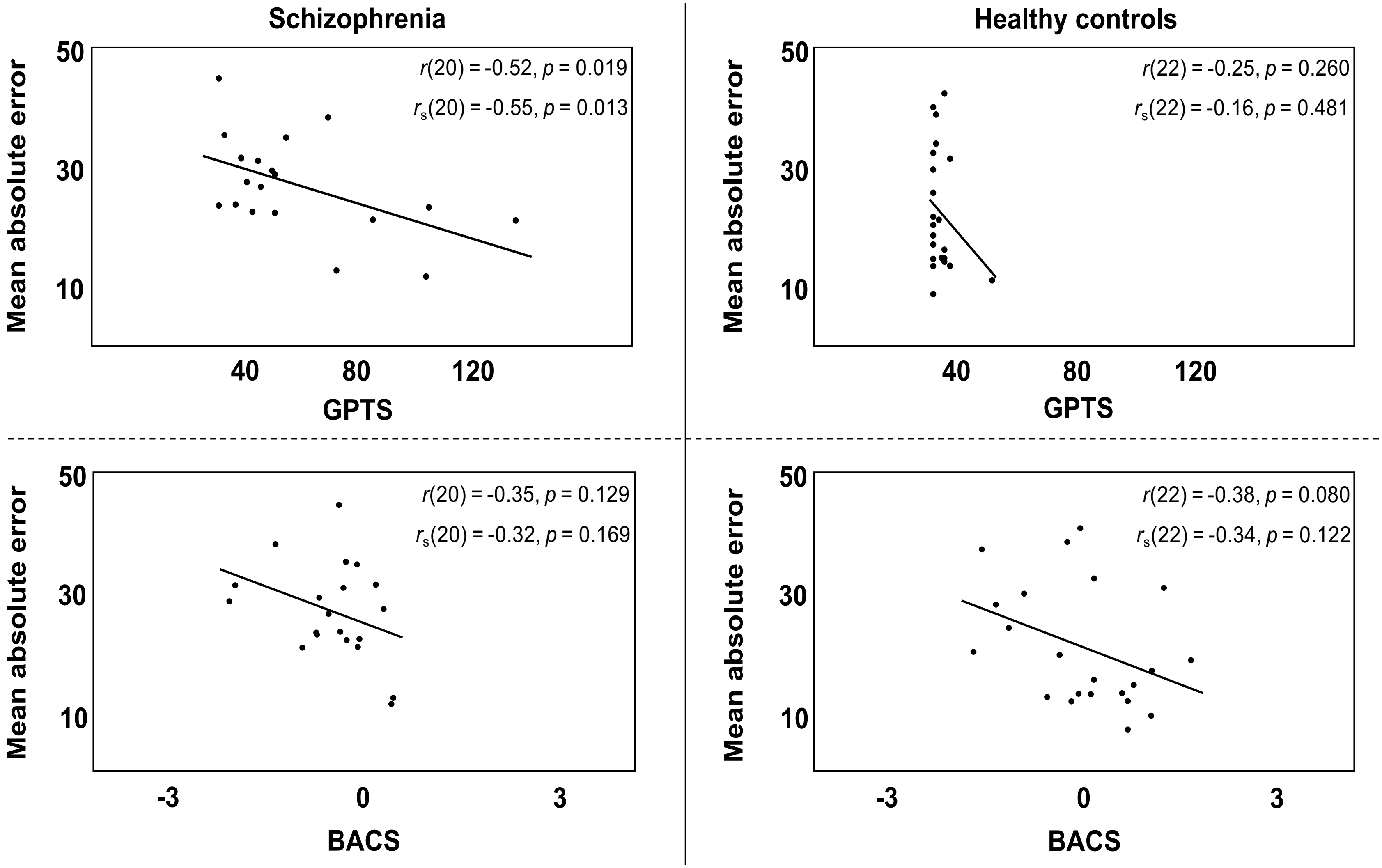
* $p < .05$ ** $p < .01$ *** $p < .001$

Figure 3.1



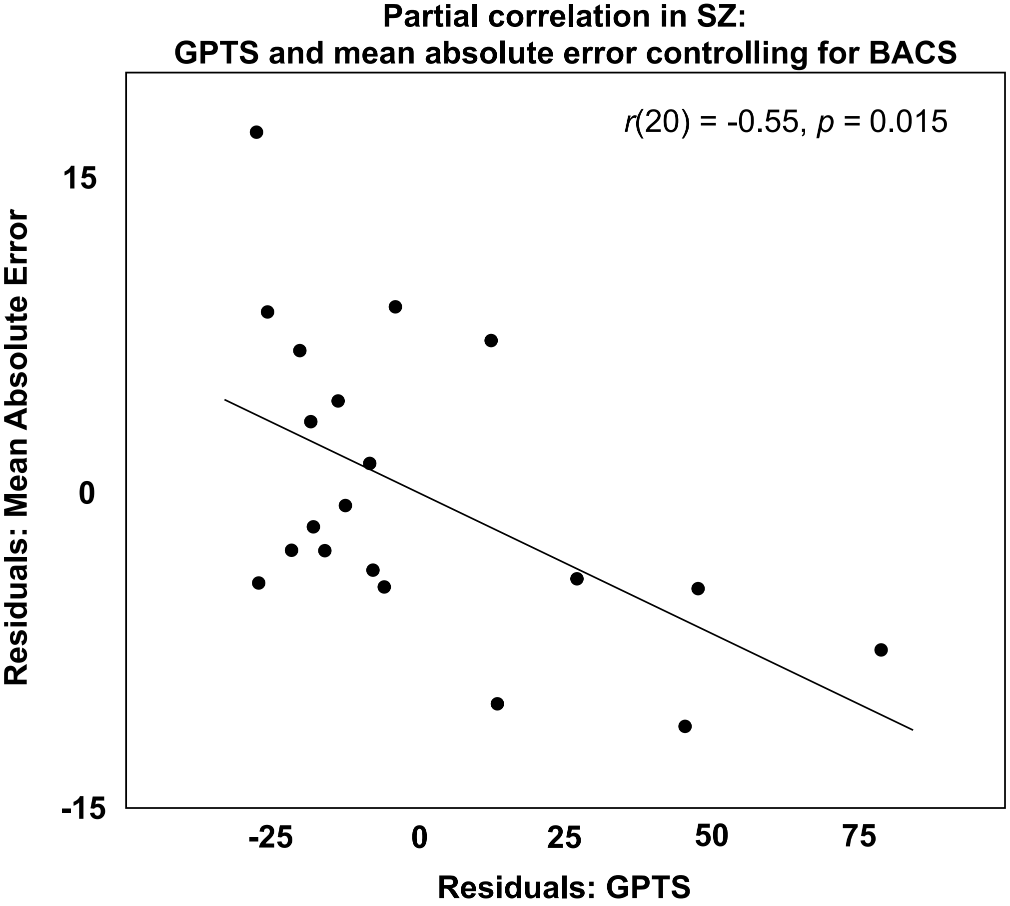
Note: Sound localization paradigm. The figure on left shows the speaker configuration used in the sound localization paradigm. There were eight active speakers (blue) and eight decoy speakers (black) on a horizontal plane elevated three feet. Each speaker was three feet away from the participant's head. The computer running the paradigm software was placed directly in front of the participant. The figure on the right shows the computer screen that participants used to identify the location of each sound via a computer mouse. The white circle in the center of the screen represents the circle of surrounding speakers. Participants could click anywhere on the white circle to identify the perceived location of each sound.

Figure 3.2



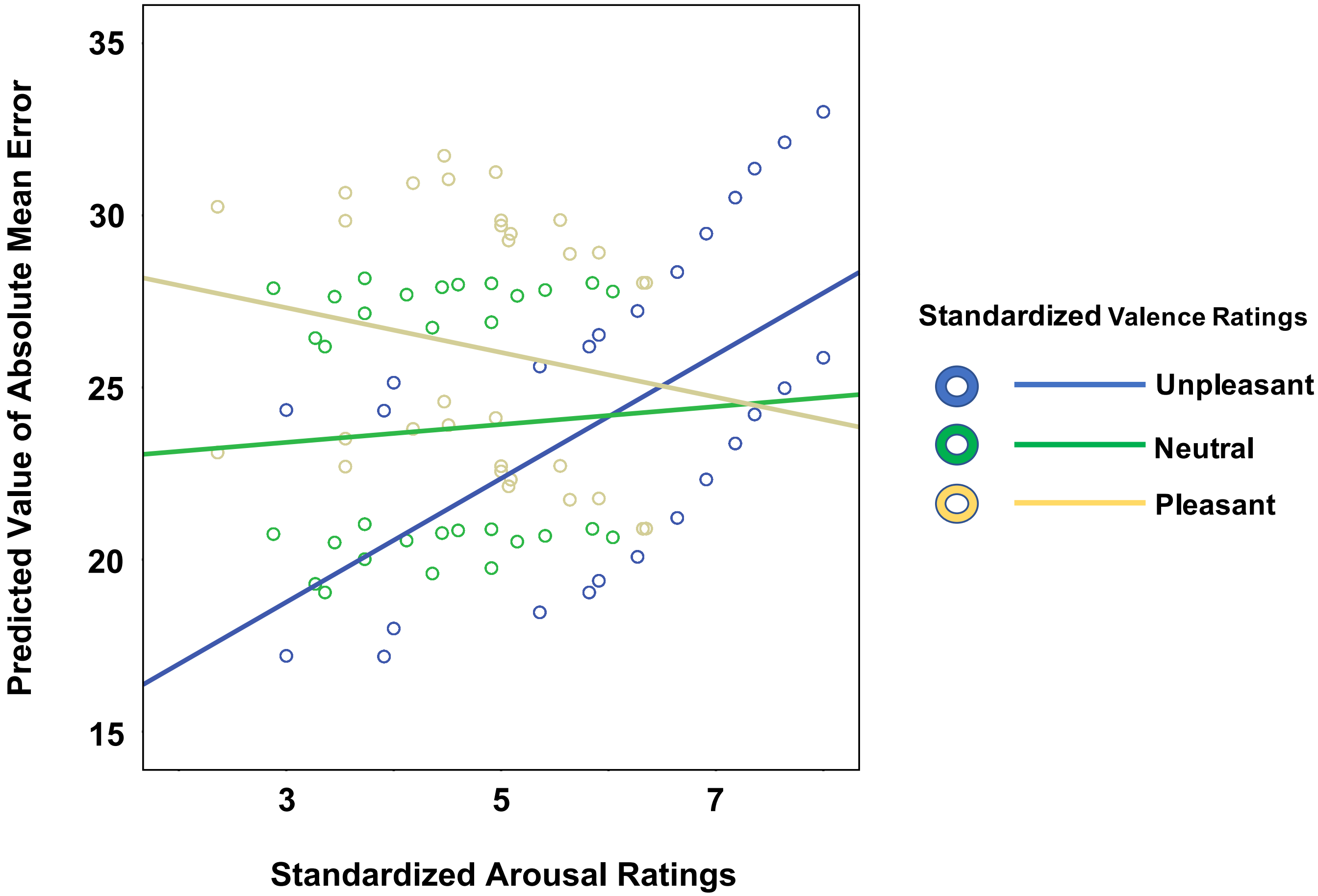
Note. Pearson and Spearman's rank-order correlations between sound localization mean absolute error and paranoia or neurocognition for each group. Pearson correlation (*r*) and Spearman's rank order correlation (r_s) are listed in the top right corner of each scatterplot. Schizophrenia are on the left and healthy controls are on the right. GPTS = Green et al. Paranoid Thoughts Scale. BACS = Brief Assessment of Cognition in Schizophrenia.

Figure 3.3



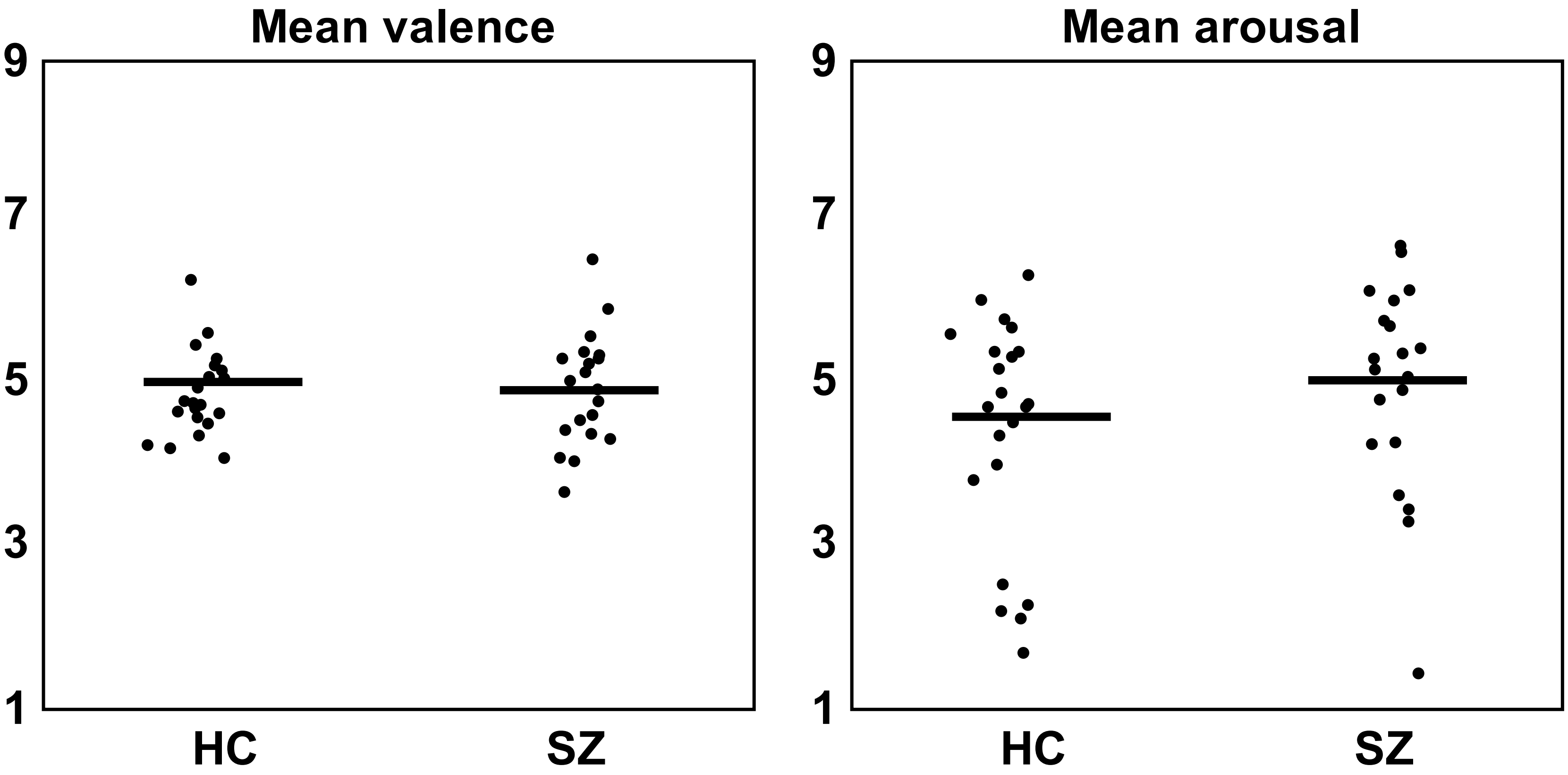
Note: Partial correlation between sound localization and paranoia while accounting for paranoia in people with schizophrenia. Scatterplot of residuals derived from simple regression analysis of the Brief Assessment of Cognition in Schizophrenia (BACS) predicting Green et al. Paranoid Thoughts Scale (GPTS) variance, along with simple regression analysis of BACS predicting mean absolute error variance in people with schizophrenia (SZ). Plotting these residuals serve as a representation of the partial correlation between GPTS and mean absolute error in SZ.

Figure 3.4



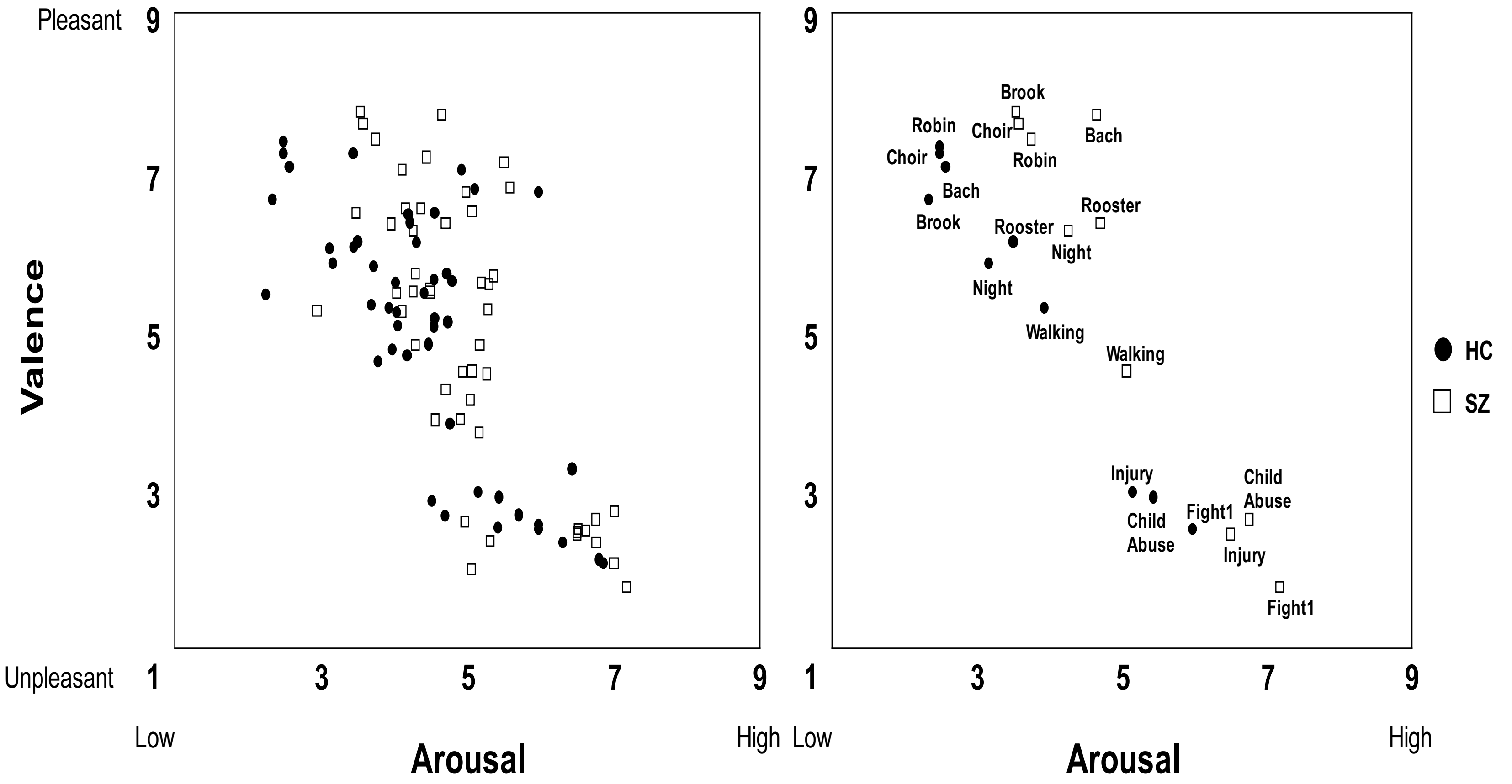
Note. Illustration of standardized valence by arousal interaction for sound localization across all participants. Interaction plot created to conceptualize the valence/arousal interaction by artificially separating valence into pleasant, neutral, and unpleasant categories using the previous cut-offs (pleasant > 5.5; neutral between 4.5 and 5.5; and unpleasant < 4.5) and preserving arousal as a continuous variable. The plot and generalized linear model showed that each one unit increase of valence (more pleasant) resulted in a 1.03 unit decrease in the strength of the relationship between arousal and absolute mean error. That is, the effect of arousal on absolute mean error decreases as valence becomes more pleasant for both SZ and HC.

Supplemental Figure 3.1



Note: Group differences in mean individual valence and arousal ratings. Left graph – Higher mean valence ratings for each group indicate more unpleasantness. Right graph – Higher mean arousal ratings for each group indicate more excitement. Bars indicate group means. There were no significant group differences for mean valence/arousal ratings of auditory environmental stimuli. One HC outlier for mean valence was removed (3 standard deviations above the group mean).

Supplemental Figure 3.2



Note: Scatterplot of group differences in mean individual valence and arousal ratings. Left scatterplot – Mean valence ratings for each IADS stimulus for SZ and HC. Right scatterplot – A total of 10 IADS stimuli with at least one rating (valence or arousal) a full point higher between groups.

CHAPTER 4

Study 3. Affective probabilistic reasoning and delusions in schizophrenia

Abstract

Biased probabilistic reasoning may contribute to delusions in schizophrenia. Despite threat often being the focus of delusions, its impact on probabilistic reasoning is unclear. In this study, 27 people with schizophrenia (SZ) and 24 healthy controls (HC) completed neutral and affective versions of a probabilistic reasoning task. Participants estimated the probability of neutral (i.e., color beads) or threatening and non-threatening (i.e., spies or civilians) sequences of confirmatory and disconfirmatory evidence coming from a likely and unlikely source. Results of linear mixed models with neurocognition as covariate showed that SZ were closer to optimal probabilistic reasoning (i.e., Bayes inference) than HC when estimating the probability of all evidence (ps < 0.05). When estimating the probability of evidence coming from the unlikely source within the affective context, SZ were closer to Bayes inference than HC in all conditions except for threatening confirmatory evidence ($p = 0.01$). Estimates closer to Bayes inference in the affective (but not neutral) context were associated with greater delusional severity in SZ. The findings suggest that probabilistic reasoning is influenced by affective contexts and related to symptomatology in SZ.

Introduction

Schizophrenia (SZ) is a chronic mental disorder characterized by delusional thinking and severe functional deficits (WHO, 2004) that may stem from a probabilistic reasoning style of overestimating and/or underestimating events relative to healthy controls (HC; Dudley, Taylor, Wickham, & Hutton, 2016). Delusional thinking may be related to a cognitive style of probabilistic reasoning that predisposes an individual to gather fewer pieces of evidence and/or disregard counter-evidence needed to challenge a belief (e.g., a 'jumping to conclusions' bias), which could lead to unlikely explanations of experiences and the formation of false beliefs (Evans, Averbeck, & Furl, 2015). Delusional thinking that is often centered on false beliefs of threat, harm, and persecution that may stem from misappraisals of threat (Freeman, 2007). For example, a person with schizophrenia may believe that a neighbor walking by their home several times indicates this person is spying on them. Yet how SZ reason in the context of threat is relatively unknown due to the focus on neutral stimuli or context in probabilistic reasoning paradigms. Few studies of SZ have investigated probabilistic reasoning in an affective (especially threatening) context. It is possible that perceived threat activates or exacerbates reasoning biases due to the need to react to threats. Thus, examination of both reasoning and threat could further our understanding of probabilistic reasoning may contribute to delusional thinking in SZ.

Nearly 70% of SZ experience ideas of persecution, suspiciousness, harm, and general paranoia (Freeman et al., 2016). This focus on threat may be related to the misappraisal of ambiguous social information as threatening, creating a false perception of danger (Freeman, 2007). Reasoning biases such as 'jumping to conclusions' are thought to protect someone from harm by making a quick decision with few pieces of evidence rather than experiencing uncertainty. Thus, it has been suggested that probabilistic reasoning biases play a role in delusional formation, as the misperception of threat from benign events could be related to an overestimation of- or inappropriate assignment of salience to unlikely events (Balzan, Delfabbro, Galletly, & Woodward, 2013; Roa Romero, Keil, Balz, Gallinat, & Senkowski, 2016). Previous reports have shown altered cognitive processes such as enhanced attention and confirmatory bias to detect threats in people with a history of delusions (Blackwood, Howard, Bentall, & Murray, 2001; Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002; Green & Phillips, 2004). Yet few studies have examined the relationship between threat and probabilistic reasoning in SZ. This is largely due to the fact that current probabilistic reasoning paradigms typically only involve affectively neutral stimuli.

For example, a paradigm known as the Beads task is most commonly used in SZ research to examine probabilistic reasoning (Huq, Garety, & Hemsley, 1988; Phillips & Edwards, 1966). In the Beads task, participants are free to draw colored beads (e.g., blue or red) that seem to come randomly from either a mainly-blue or mainly-red bead jar, each with opposite ratios of colored beads (e.g., 85 blue beads and 15 red beads in the mainly-blue jar). Participants decide the jar of origin for this seemingly random sequence of beads (sequences are predetermined). SZ tend to make fewer draws relative to HC and decide on a jar of origin after 1-2 beads are drawn, indicative of the jumping to conclusions bias, which may occur in up to 30-40% of SZ (Garety et al., 2013). However, the findings on the relationship between draws to decision and severity of delusions have been mixed. There is evidence that SZ with greater delusional severity make even fewer draws than those with attenuated delusions (Moritz & Woodward, 2004), however, evidence also suggests that is no relationship between draws to decisions and delusional severity in SZ (Colbert, Peters, & Garety, 2010; Menon, Pomarol-Clotet, McKenna, & McCarthy, 2006).

It should be pointed out that requiring fewer pieces of evidence prior to deciding could be considered a more logical probabilistic reasoning style from the Bayesian perspective. For instance, using the previous example, if the first bead presented is blue, then there is an 85% probability that beads are coming from the mainly-blue jar. The first blue bead and any blue beads that follow would be considered confirmatory evidence for the hypothesis that the beads come from the mainly-blue jar. If the second bead presented is also blue, it would indicate a 97% probability that the beads are coming from the mainly blue jar. Thus, even a 3% chance of error is too high for HC to feel confident to make a decision. This is in contrast with an 85% probability that the beads are coming from the mainly-blue jar instilling enough confidence for some SZ to decide after one draw.

Considering the possible link between fewer bead draws and greater delusional severity, an increased data-gathering approach to probabilistic reasoning that is characteristic of HC (i.e., drawing well over 1-2 beads) may be more appropriate in everyday situations, as underestimating the probability of likely events and overestimating the probability of unlikely events relative to optimal Bayes inference, may promote data gathering and adjustment of beliefs. This style of probabilistic reasoning that is characteristic of HC could be considered “conservative.” Estimates that are closer to optimal Bayes inference and more typical of SZ during the Beads task could lead to resolute decisions based on few pieces of evidence. This could be relevant to the appraisal of threat within the environment, as quick decisions could have advantages in reacting to danger. In addition, a graded estimates version of the Beads task provides further insight into probabilistic reasoning, as it has a similar design but requires participants to provide an estimate of the likely source of beads after each bead presentation. For example, rating a 0 to 100 probability that the beads are coming from the mainly-blue jar (Moritz & Woodward, 2005; Moritz, Woodward, & Lambert, 2007). In this version of the task, one study has shown that SZ with severe delusions (*n* = 5) provide higher estimates of the likely source (i.e., near or above Bayes inference) than HC (*n* = 35) or SZ without delusions (*n* = 25), even after one piece of evidence, along with overadjustment (decreased probability estimate that is closer to HC and Bayes inference) to a single piece of disconfirmatory evidence relative to HC (Speechley, 2010). While the size of severe delusions group in the study is relatively small, the findings suggest that estimating closer to- or above Bayes inference, could predispose SZ to more severe delusional thinking, as estimates that are near or above Bayes inference and less "conservative" than HC could lead to reduced data-gathering to challenge a belief, especially in the context of perceived threat. Overadjustment to a single piece of disconfirmatory evidence could be indicative of a substantial change in the appraisal of threat. For example, a well-known neighbor accidently damages your mailbox by backing into it with their car and now becomes a potential threat based on this one piece of evidence despite no prior evidence of being a threat (Moritz & Woodward, 2005).

Yet the Beads task and its current variations may not tap into the threat that often accompanies delusional thinking. For instance, an affective version of the Beads task substitutes beads for words (e.g., “annoying” or “kind”) drawn from one of two surveys containing a mix of negative and positive words that describe the participant (Dudley, John, Young, & Over, 1997; Warman, Martin, & Lysaker, 2013). While this version of the traditional Beads task does contain a threat to the participant’s self-image, it may not evoke a threat of being harmed by others that is characteristic of delusional thinking (Freeman, 2007) and has not been adapted as a graded estimates task. Another version of a graded estimates task known as the Fish task includes fish drawn one of two lakes instead of beads drawn from one of two jars (Speechley, 2010). However, such stimuli (i.e., words and fish) may not reflect real world situations involving perceived threat in social settings. As such, this may help to explain why a recent meta-analysis found no correlation with traditional Beads task performance and delusional thinking in SZ (Ross, McKay, Coltheart, & Langdon, 2015). A separate meta-analysis found only a trend-level association (*r* = -.09) between number of draws and severity of delusions (Dudley et al., 2016).

Additionally, the Beads, Words, and Fish tasks traditionally ask for probability estimates of the likely source (P) only and assume that participants’ estimates for the unlikely source would be 1 – P (e.g., if a participant estimates a 60% probability for the likely source, a 40% probability estimate for the unlikely source would be assumed). However, by obtaining estimates for both possible sources, research has shown less “conservative” estimates in SZ with severe delusions compared with HC for the likely source but not the unlikely source, along with comparable estimates of unlikely events in SZ with severe delusions and HC (Speechley, 2010). Overall, there is a need for probabilistic reasoning paradigms to not only tap into threat, but to also include probability estimates of both sources (i.e., likely and unlikely). The findings could help to better understand probabilistic reasoning styles that may contribute to the formation and maintenance of delusions related to threat in SZ.

The current study examined probabilistic reasoning in people with schizophrenia and a history of delusional thinking and those with no psychiatric history using neutral and affective versions of a graded estimate task. We examined probabilistic reasoning by comparing participants' probability estimates of both the likely and unlikely source when presented with neutral or threatening and non-threatening confirmatory and disconfirmatory evidence against estimates obtained using the Bayes' rule. It was predicted that SZ would demonstrate a general pattern of estimates closer to Bayes inference than HC for both versions of the task (i.e., HC would appear "conservative" relative to SZ and Bayes inference via underestimation of likely events and overestimation of unlikely events). We explored differences in probability estimates in SZ compared with HC differed according to stimuli and evidence type (e.g., confirmatory spies versus disconfirmatory civilians) for likely and unlikely sources. Within SZ, it was predicted that there would be a significant relationship between probabilistic reasoning closer to- or above Bayes inference and more severe delusional thinking for the affective version of the task only.

Methods

Participants

Participants were recruited from University of Michigan Department of Psychiatry and Psychology research registries (*N* = 51). Inclusion/exclusion criteria for healthy control participants (*n* = 24) included no history of: 1) a Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association, 2000) Axis 1 disorder according to the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997), 2) immediate family members with a psychotic or bipolar disorder, and 3) a major medical condition that may impact cognitive function (e.g., traumatic brain injury or seizures). A total of 27 patient participants had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and history of delusional thinking confirmed by SCID-IV. Patient participants did not have a history of substance abuse or dependence within the last five years.

Procedure

Participants were assessed with the SCID-P or SCID-NP administered by a clinical psychology doctoral student. All participants completed the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe, 1999) as a measure of general cognition. Severity of delusional thinking in SZ was determined with the delusions subscale of the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Participants then completed the graded estimates probabilistic reasoning tasks. Participants also completed similar tasks adapted for the event-related brain potential (ERP) technique in a later session. The ERP results are not reported here. The study protocol was approved by the University of Michigan Institutional Research Board. All participants provided informed consent prior to enrolling in the study.

Graded Estimates Tasks

Participants were seated in front of a Windows desktop computer and randomly assigned to first complete either a neutral or affective version of a graded estimates task. The task required participants to determine how likely it was that a sequence of stimuli was coming from one of two sources. For the neutral version of the task, participants were told that there are two jars, each with 100 beads. One jar contains 60 orange beads and 40 violet beads while the other contains 40 orange beads and 60 violet beads; the beads are randomly dispersed within the jars. A 60/40 ratio was chosen since SZ typically have fewer draws to a decision in a Beads task with a 60/40 ratio compared with the more common 85/15 ratio (Ross et al., 2015). Participants were then told that one of the jars has been chosen at random and a series of beads will be shown from this chosen jar. These beads always come from the chosen jar and are replaced after being drawn so that the proportion of beads in both jars stays the same. Participants rated the probability on a continuous scale of 0 to 10 that the series of beads came from the mainly-orange jar (i.e., 0 = very unlikely and 10 = very likely). Using an identical scale, participants also rated the probability that the series of beads came from the mainly-violet jar. Participants used a computer mouse to indicate their estimate on the two scales (i.e., participants could click anywhere on the scales to make their ratings). Thus, the current paradigm does not assume that estimates of each jar sum up to 10. In other words, an estimate of 6/10 or 60% probability for the mainly-orange jar does not necessarily mean an expected estimate of 40% probability for the violet jar; a participant could estimate 60% for the mainly-orange jar and 50% for the mainly-violet jar. This allows for further examination of probabilistic reasoning that is free of assumed complementary estimates for likely and unlikely sources. MATLAB software (MathWorks, Inc.) was used to run the paradigm.

Each trial began with the presentation of an orange or purple bead. Participants then provided an estimate that the current bead comes from the mainly-orange jar and then an estimate that current bead comes from the mainly-violet jar. There was no time limit. Immediately after providing these estimates, a second bead appeared, and the previous bead was placed near the top of the computer screen to serve as a reminder of the previously drawn beads. Participants then provided an estimate that the two beads came from the mainly-orange jar and then an estimate that the two beads came from the mainly-violet jar. This procedure continued until ten beads were shown and then a new sequence of beads began. See Supplemental Figure 1 for a screenshot of the task. A total of six predetermined sequences were presented once in a random order:

(1A) O O O O O O O O O O (ten orange beads)
(1B) V V V V V V V V V V (ten violet beads)
(2A) O O O O V O O O O V (eight orange and two violet beads)
(2B) V V V V O V V V V O (eight violet and two orange beads)
(3A) O O V O O O O V O O (eight orange and two violet beads)
(3B) V V O V V V V O V V (eight violet and two orange beads)

Each of the three kinds of sequences (i.e., 1, 2, and 3) were counterbalanced for the different stimuli (i.e., orange or violet beads). That is, A and B had the same pattern but swapped bead colors. All sequences were designed so that one of the jars is more likely than the other. For example, Sequence 1A included only orange beads, firmly establishing a hypothesis that the beads are coming from the mainly-orange jar. According to Bayes theorem, which provides a mathematical calculation to determine optimal probabilistic reasoning via adjustment of prior knowledge or predictions based on new or current evidence (Bayes, 1763; Hemsley & Garety, 1986; Laplace, 1902), there is a 60% probability for the likely source being the mainly-orange jar at the presentation of the first bead in Sequence 1A. This probability increases to 98.3% by the presentation of the tenth consecutive orange bead. Sequences 1A and 1B allow for a better understanding of how HC and SZ reason in the context of mounting confirmatory evidence for the hypothesis. Sequences 2A, 2B, 3A, and 3B were designed to establish a clear hypothesis for the likely stimuli source despite occasional disconfirmatory evidence. For example, in Sequence 2A the first bead is orange, which provided support for the hypothesis that beads come from the mainly-orange jar. The first orange bead is then followed by three consecutive orange beads that provided more support for this hypothesis (83.5% probability at that point). The first presentation of a violet and thus disconfirmatory piece of evidence only reduced the probability of the series of beads came from the mainly-orange jar to 77.1%, and the presentation of four additional and consecutive beads increased this probability to 94.5% before the final bead, which was violet and disconfirmatory, only reducing the probability of the series of beads came from the mainly-orange jar to 91.9%. Further, Sequences 2A, 2B, 3A, and 3B were designed to include two pieces of disconfirmatory evidence at seemingly random points, but always with the presentation of at least two pieces of confirmatory evidence prior to disconfirmatory. These four sequences allowed for a better understanding of probabilistic reasoning in the context of mixed evidence while still establishing a favored hypothesis for the likely source of stimuli.

For the affective version of the task, beads and jars were replaced by spies/civilians and buildings, respectively. The stimuli were obtained from the AR Face Database and used with the owner's permission (Martinez & Benavente, 1998). Participants were told that that are two buildings, each with 100 people inside. One building contained 60 spies and 40 civilians while the other building contained 40 spies and 60 civilians. To distinguish between spies and civilians, spies always wore sunglasses and civilians never wore sunglasses. All spies/civilians were Caucasian males to reduce a possible effect of race and sex. Participants were told that spies *may* be spying on them and that civilians were never spying on them. The instructions were identical to the neutral version of the task, with participants determining the probability of people, either spies or civilians, coming from a building with mainly spies (60 spies and 40 civilians) and a building with mainly civilians (60 civilians and 40 spies). See Supplemental Figure 2 for a depiction of the task. The sequences used in the affective version of the task were the same as the neutral version of the task:

(1A) S S S S S S S S S S	(ten spies)
(1B) C C C C C C C C C C	(ten civilians)
(2A) S S S S C S S S S C	(eight spies and two civilians)
(2B) C C C C S C C C C S	(eight civilians and two spies)
(2C) S S C S S S S C S S	(eight spies and two civilians)
(2D) C C S C C C C S C C	(eight spies and two civilians)

To ensure participants understood the task instructions, a practice session consisting of one sequence of ten random beads (orange or violet) or spies/civilians was completed prior to the actual tasks. For example, stimuli in the practice session were comprised of beads if the participant was randomly selected to complete the beads version of the task first; practice session stimuli were spies/civilians if the participant was randomly selected to complete the affective version first.

Data aggregation for graded estimate tasks

To determine the deviation of estimates from optimal Bayes inference in both versions of the task, each of the 20 estimates in every sequence (i.e., ten for the likely source and ten for the unlikely source) were first multiplied by ten (i.e., an estimate of 7.5 becomes 75). Bayes theorem calculation was then subtracted from the corresponding probability, resulting in an ‘estimate deviation’ from Bayes inference. For example, if a participant’s sequence of estimates for the likely source in Sequence 1A is 65, 68, 75, 80, 85, 90, 95, 100, 100, and 100, these estimates were subtracted from corresponding Bayes theorem calculations of 60, 69.2, 77.1, 83.5, 88.4, 91.9, 94.5, 96.2, 97.5, and 98.3, respectively. Thus, estimate deviation with a positive value indicates overestimation (e.g., 65 – 60 = 5) and an estimate deviation with a negative value indicates underestimation relative to Bayes inference (e.g., 68 – 69.2 = -1.2). Estimate deviation was calculated according to variables of interest (e.g., confirmatory and disconfirmatory evidence types) to run separate LMM for estimate deviation of likely and unlikely sources in the neutral and then affective versions of the task.

For the neutral version, estimate deviations for the likely source of Sequence 1A was averaged across the ten trials since all stimuli were confirmatory pieces of evidence (i.e., continuing with the previous example, the average of 5, -1.2, -2.1, -3.5, -3.4, -1.9, 0.5, 3.8, 2.5, and 1.7 results in an estimate deviation of 0.14 for the likely source of Sequence 1A). This was repeated for the unlikely source of Sequence 1A. Since the sequence of beads was identical for Sequence 1A and 1B, and bead color (i.e., orange or violet) was not a variable of interest, Sequence 1A and 1B were averaged together for the likely source and then the unlikely source and referred to as the neutral Consistently-Confirmatory Sequence, with an average estimate deviation for the likely source and an average estimate deviation for the unlikely source. For the ten trials within neutral Sequence 2A, 2B, 3A, and 3B, estimate deviations for the eight confirmatory and two disconfirmatory stimuli were averaged. All four sequences were then averaged for both the likely and unlikely source due to bead color or order of disconfirmatory evidence not being variables of interest. These combined sequences are referred to as the neutral Mixed Sequence. After all averages were calculated for neutral Consistently-Confirmatory and Mixed Sequences, there were six estimate deviations for each participant.

For the affective version of the task, calculation of estimate deviation was similar to the neutral version of the task, except that in this version of the task stimuli type (spy or civilian) was a variable of interest. Thus, the ten estimates for the likely building in affective Sequence 1A were averaged separately from those for the likely building in Sequence 1B. The same was done for the unlikely building in Sequence 1A and then Sequence 1B. Affective Sequences 1A and 1B were referred to as the affective Consistently-Confirmatory Sequence. Since affective Sequences 2A and 3A include the mainly spy building as likely, the estimates in these sequences were averaged together according to confirmatory (spies) and disconfirmatory evidence type for the likely building. The same was done for the unlikely building in Sequences 2A and 3A. Affective Sequences 2B and 3B include the mainly civilian building as likely and estimates in these sequences were also averaged together and according to evidence type. The same was done for the unlikely building in Sequences 2B and 3B. Affective Sequences 2A, 2B, 3A, and 3B were referred to as the affective Mixed Sequence. After all averages were calculated for affective Consistently-Confirmatory and Mixed Sequences, there were 12 estimate deviations for each participant.

Data Analysis

Simple *t*-tests or chi-square were used to determine group differences in demographics and self-report measures (Table 1).

For the graded estimates tasks, data for two SZ participants were removed due to random performance reported by the participants and observed by the study team during the tasks. In addition, estimate outliers (three standard deviations from the mean) were removed from analyses (~1% of data). The Consistently-Confirmatory Sequence was examined separately from the Mixed Sequence due to the different research questions they answer (i.e., Sequence 1 examines probability in the absence of disconfirmatory evidence and Sequence 2 includes both confirmatory and disconfirmatory evidence). Due to collinearity between likely and unlikely sources, the likely and unlikely source was examined separately. Neurocognition (e.g., working memory) has been associated with probabilistic reasoning in SZ (Batty et al., 2016; Garety et al., 2013; Menon et al., 2006) and was included as a covariate in all analyses of estimate deviation group differences. Since a random and/or repeated factor was not available for the neutral version of the Consistently-Confirmatory Sequence, a one-way analysis of covariance (ANCOVA) was used to determine group differences in the estimate deviation of the likely and unlikely jars while accounting for neurocognitive covariance, resulting in two one-way ANCOVAs. All other sequences were examined with linear mixed models (LMM) predicting variance of estimate deviation for the likely and unlikely source (jars or buildings) in the Consistently-Confirmatory Sequence (affective version) and the Mixed Sequence (neutral and affective versions), resulting in six models. LMM included a random intercept for participant ID and repeated effect(s) for evidence type (and stimuli type for the affective version only). In comparison to traditional repeated-measures ANOVA, LMM help reduce the risk of Type I errors by selecting the simplest model with the best fit to the data rather than the ANOVA approach of examining all possible main effects and interactions without correction for multiple comparisons (Demidenko, 2013). Separate LMM were created for the likely and unlikely sources due to collinearity.

The one-way ANCOVA used for likely jar of the neutral Consistently-Confirmatory Sequence included group (HC or SZ) as a fixed effect and estimate deviation as the dependent variable. This ANCOVA model was repeated for the unlikely jar of the neutral Consistently-Confirmatory Sequence. The first LMM for the likely jar of the neutral Mixed Sequence included group and evidence type (confirmatory or disconfirmatory) as fixed effects, BACS as covariate, and evidence type as the repeated measure. This model was repeated for the unlikely jar of the neutral Mixed Sequence. The first LMM for the likely building of the affective Consistently-Confirmatory Sequence included group and stimuli (spy or civilian) as fixed effects, BACS as a covariate, and stimuli as the repeated measure. This model was repeated for the unlikely building of the affective Mixed Sequence. The first LMM for the likely building of the affective Mixed Sequence was identical to the LMM of the affective Consistently-Confirmatory Sequence except that evidence type was added as a fixed effect and repeated measure. This LMM was repeated for the unlikely building of the affective Mixed Sequence. LMM convergence errors were observed due to collinearity between confirmatory and disconfirmatory evidence, along with spies and civilians for the affective version. Since this violates an assumption of LMM, convergence errors were resolved by removing the repeated factor(s) from the final model. Accordingly, all models were compared with and without the repeated factor(s) and the final winning model was selected based on the information criterion (-2 REML log-likelihood, AIC, and BIC). Within each ANCOVA or LMM, main effects were included first, followed by two-way interactions, and then higher-order interactions. Only significant interactions were included in the final model (i.e., all nonsignificant interactions were removed) and interaction contrast was used for post-hoc analysis of significant higher-order interactions.

Pearson and Spearman's rank-order correlations were used to determine relationships between SAPS delusions and mean estimate deviation of Consistently-Confirmatory and Mixed Sequences (neutral and affective versions), along with significant main effects and/or interactions of estimate deviations derived from LMM (e.g., confirmatory civilians).

Results

Figure 1 shows the pattern of probability estimates between SZ and HC for all sequences. ANCOVA and LMM showed a significant group difference in estimate deviation for neutral and affective likely and unlikely sources in both neutral and affective task versions of the Consistently-Confirmatory Sequence (i.e., only confirmatory evidence), along with BACS being a significant covariate in all models (Table 2). Specifically, relative to Bayes inference, HC underestimated probabilities for likely events and overestimated probabilities for unlikely events, while SZ had a similar but weaker pattern of probability estimates (i.e., HC were provided “conservative” estimates relative to SZ and Bayes inference).

LMM showed that for the likely and unlikely jars and buildings in the Mixed Sequence, there was also a similar significant group difference, along with BACS as a significant covariate. For the unlikely jar in the neutral Mixed Sequence, along with likely and unlikely buildings in the affective Mixed Sequence, there was a significant interaction between evidence type and BACS (Table 3). Across participants, poorer BACS was associated with increased estimates for unlikely events in the neutral and affective Mixed Sequences and decreased estimates for likely events in the affective Mixed Sequence, and this relationship was accentuated for disconfirmatory compared with confirmatory evidence (Figure 2). For the unlikely building in the affective Mixed Sequence, there was a significant three-way interaction between group, evidence type, and stimuli (Figure 3). Interaction contrast showed that SZ and HC provided similar ratings for confirmatory evidence when threatening (i.e., spy) in comparison to all other evidence/stimuli types combined, $t(122.2) = -2.58$, $p = 0.011$).

Figure 3 also shows the significant Pearson and Spearman’s rank order correlations between estimate deviation related to the LMM interaction identified in the affective Mixed Sequence (Group x Stimuli x Evidence) and SAPS Delusions in SZ.

There was a significant positive Pearson and Spearman's rank order correlation between SAPS delusions and estimate deviation of confirmatory spies, along with the average estimate deviation of the three evidence type/stimuli combined (i.e., confirmatory civilians; disconfirmatory spies and civilians). There was also a positive Pearson and Spearman's rank order correlation between SAPS delusions and mean estimate deviation for the likely and unlikely buildings in the affective Mixed Sequence but not the likely and unlikely jars in the neutral Mixed Sequence (Figure 4). In all correlations, greater delusional severity was related to overestimation of likely events and underestimation of unlikely events. There were no significant correlations between SAPS Delusions and the neutral or affective Consistently-Confirmatory Sequence estimate deviations in SZ (*p*'s > 0.05; Supplemental Table 1).

Discussion

The current study examined probabilistic reasoning in people with schizophrenia and those with no history of mental illness using neutral and affective versions of a graded estimates task in which participants estimated the probability of neutral (i.e., color beads) or threatening and non-threatening (i.e., spies or civilians) sequences of confirmatory and disconfirmatory evidence coming from a likely and unlikely source. It was found that in both task versions, SZ estimated closer to optimal or accurate probabilistic reasoning (i.e., Bayes inference) than HC. This pattern of estimation for HC could be described as "conservative" relative to SZ and Bayes inference. However, there was one exception to this finding, SZ was not significantly different from HC when estimating the probability that a sequence of affective evidence was coming from an unlikely source for all combinations of evidence and stimuli (e.g., confirmatory civilians) except for the condition when confirmatory evidence was threatening (i.e., spies). That is, all participants had less “conservative” estimates for evidence that confirmed spies were not coming from an improbable source. In addition, poorer neurocognition was associated with a conservative style of probabilistic reasoning across all participants, especially for disconfirmatory compared with confirmatory evidence. Within SZ, a less conservative style of probabilistic reasoning was related to greater severity of delusional thinking.

While most people do not explicitly use Bayes inference in everyday situations that require probability, as evidenced by the conservative pattern of probability relative to Bayes inference in the current study and previous reports (Evans, 1989; Garety & Freeman, 1999; Tversky & Kahneman, 1974, 1983), the current findings provide support for Freeman’s cognitive model of delusions in which estimates closer to Bayes or extreme initial estimates may predispose individuals to ‘jump to conclusions’ while conservative estimates (i.e., underestimation of likely events and overestimation of unlikely events) may protect individuals from jumping to conclusions that are false or delusional (Dudley & Over, 2003). That is, healthy individuals may be more skeptical of the likelihood of events relative to SZ and thus ‘hold conclusions’ prior to forming beliefs. Considering that Freeman’s model can be used to understand the formation of delusions in clinical settings (Cognitive-Behavioral Therapy for Psychosis; Fowler, Garety, & Kuipers, 1995), the current findings provide support for the psychosocial treatment of biases probabilistic reasoning in SZ such as jumping to conclusions.

Freeman’s model also identifies affect as contributing to the formation of delusions (e.g., anxiety may heighten anticipation of danger and promote a jumping to conclusions bias). The current study provides additional support for Freeman's model of delusions with the finding of HC estimating closer to SZ and Bayes inference for affective evidence that confirmed threatening evidence (i.e., spies) were not coming from an improbable source. Otherwise, HC provided conservative estimates for confirmatory civilians and disconfirmatory civilians or spies relative to SZ and Bayes inference. For HC, this may underscore the influence of threat on probabilistic reasoning within an affective context, as spy stimuli may tap into threats relevant to the current era of government surveillance (NSA phone monitoring; Rainie & Madden, 2015) and promote a style of probabilistic reasoning that is characteristic of SZ.

A more comprehensive model of delusional formation has been proposed by Adams, Stephan, Brown, Frith, and Friston (2013) in which delusional thinking is the result of aberrant precision or confidence of beliefs. Adams and colleagues posit that a belief can be held with varying levels of precision or confidence. A belief held prior to observing evidence is a prior belief and is updated as the posterior belief after the observation of evidence (i.e., combination of prior beliefs with sensory evidence). Precision errors may stem from neuromodulatory dysconnections at the synaptic level, primarily in the prefrontal cortex and medial temporal lobe (e.g., abnormal neuromodulation of superficial pyramidal cells). Yet this theory does not fully address the contribution of affect to the process of belief and sensory evidence precision, as the current study found that an affective context influences probabilistic reasoning for those with no history of mental illness.

Among all participants, poorer neurocognition was related to increased probability estimates of unlikely events and decreased probability estimates of likely events, and this relationship was stronger for disconfirmatory compared with confirmatory evidence. This finding may seem to contradict the previous finding of group differences in estimate deviation, as HC but not SZ tended to demonstrate the previously described pattern of estimation, yet SZ have poorer neurocognition than HC. However, the *intercept difference* of the regression line between SZ and HC, along with the range of estimate deviations and BACS observed in Supplemental Figure 3, help to explain this finding. Supplemental Figure 3 shows that HC estimated closer to Bayes inference as BACS improved while SZ estimated farther from Bayes as BACS improved *or* worsened, with no interaction between group and BACS. It is necessary to note that the intercept value is generally farther from Bayes inference for HC but closer to Bayes inference for SZ. HC typically overestimated unlikely events and underestimated likely events compared with SZ (i.e., HC were more “conservative” relative to SZ and Bayes inference), the conservative pattern decreased as BACS improved for HC and thus brought HC closer to Bayes inference. But for SZ, since they typically estimated closer to Bayes inference, improved BACS moved SZ farther from Bayes inference via underestimation of unlikely events and overestimation of likely events. Thus, it would be inaccurate to conclude that those with higher neurocognition estimate closer to Bayes inference, instead this finding suggests that those with higher neurocognition tend to use a less conservative reasoning style compared with those with lower neurocognition, especially for disconfirmatory compared with confirmatory evidence. That is, an unlikely event becomes more likely and a likely event becomes even less likely after the presentation of disconfirmatory compared with confirmatory evidence for those with poorer neurocognition. It is possible that poorer working memory could impact the ability to recall previous estimates and lead to an emphasis on current evidence, resulting in an unlikely event becoming more likely and a likely event becoming less likely when presented with disconfirmatory evidence. However, previous studies have reported mixed results regarding the relationship between neurocognition and probabilistic reasoning in SZ using the traditional Beads task. While poorer neurocognition has been associated with a reduced draws to decision or heightened ‘jumping to conclusions’ bias in SZ (Garety et al., 2013), it has also been associated with more draws to decision in SZ (Batty et al., 2016). Few studies (if any), have examined the relationship between graded estimates and neurocognition. As current evidence remains inconclusive, future probabilistic reasoning studies in SZ would benefit from analysis of neurocognition and evidence types to better understand this relationship.

Decreased probability estimates of unlikely events and increased estimates of likely events were related to more severe delusional thinking in SZ, and not just for confirmatory spies, but affective sequences in general. The positive correlations observed between less “conservative” probability estimates of affective but not neutral evidence and more severe delusional thinking in SZ appear to support Freeman’s inclusion of affect into his model of delusional formation. It is possible that the fear/anxiety elicited by threat need to quickly respond to a possible threat within the environment promotes a need to respond quickly and a ‘jumping to conclusions’ bias that could lead to false beliefs (Freeman, 2007). Previous reports have observed a heightened jumping to conclusions bias in SZ using self-referent words that may threaten self-image in place of beads during the traditional Beads task (Dudley et al., 1997), suggesting that affective stimuli or contexts with some type of threat promote higher probability estimates of likely events and lower probability estimates of unlikely events. Considering the observed relationship with delusional thinking in SZ and probability estimates of affective stimuli only, the current findings suggest that the weak or nonsignificant relationship between delusional severity and draws to decisions in the Beads task reported in meta-analyses (Dudley et al., 2016; Ross et al., 2015) may be explained by the use of neutral rather affective stimuli. It is possible that benign stimuli within an affective context may be perceived as threatening (e.g., civilians could be misinterpreted as spies), similar to the aberrant salience model of psychosis (Morrison & Murray, 2009).

The current findings do not replicate all findings from Speechley (2010), one of the only other SZ studies to use a probabilistic reasoning task with estimates for the likely *and* unlikely source of evidence. Speechley (2010) reported that SZ with severe delusions had similar estimates to HC for unlikely events but higher estimates than HC for likely events (i.e., overestimation for both events relative to Bayes inference), and SZ without delusions estimated similar to HC for both sources. In this study, SZ estimated significantly closer to Bayes inference than HC for both the likely and unlikely source of evidence. It is possible that differences in task design contributed to this discrepancy. Speechley (2010) used unique ratios for most sources (e.g., 80 black fish / 20 white fish for the likely source and 50 black fish / 50 white fish for the unlikely source) compared with the current study, which used inverse ratios for the likely and unlikely sources (i.e., 60/40 for the likely source and 40/60 for the unlikely source). Further, Speechley (2010) had participants view the sources without being told the ratio of fish for each source. Both factors could have impacted probability estimates for the unlikely source in comparison to the current study, especially when considering the ambiguity that could arise with a 50/50 source option. That is, participants may have found it difficult to consider a 50/50 source option as unlikely. We also did not observe overadjustment in probability estimates for a single piece of disconfirmatory evidence in SZ relative to HC. This could be explained by differences between study samples, as the current sample had relatively low levels of delusional severity compared with those with severe delusions reported in Speechley (2010), inpatient participants reported in Garety, Hemsley, and Wessely (1991), or a majority of participants with active or severe delusions reported in Langdon, Ward, and Coltheart (2010). It is possible that SZ with more severe symptomatology demonstrate a cognitive style of probabilistic reasoning that emphasizes a single piece of current evidence rather than the accumulation of evidence, resulting in overadjustment.

Limitations

The current study is limited by a relatively small sample size, along with a limited range of delusional severity in patients. Speechley (2010) found that only SZ with currently severe delusional thinking exhibited hypersalience to evidence hypothesis matches, however, the small sample of those with severe self-reported delusional thinking raises questions about the generalizability of the finding (*n* = 5). The current study may have benefited from the addition of a decision point to the paradigm, which would have allowed for a JTC determination (i.e., draws to decision) to compliment probability estimates. It is possible that those who are more prone to JTC (i.e., 1-2 draws to decision) have a stronger relationship between probability estimates and delusional thinking within the context of hypersalient evidence-hypothesis matches.

However, there are also methodological issues concerning the current paradigm used to index probabilistic reasoning (i.e., the traditional Beads Task and its modified versions) that includes participants' miscomprehension of the task '(e.g., participants doubt the evidence is coming from one source). A recently developed and methodologically sound alternative to the Beads task is the Box task, which may benefit from adaption with affective stimuli (Moritz et al., 2017). Further, the effects of reward, punishment, psychological stress, or time constraints were not evaluated in the current study. All of these factors could impact probabilistic reasoning, even more so within the current affective paradigm. In addition, it is unknown if the current stimuli elicit threat due to the absence of participant ratings of elicited threat for the stimuli (e.g., 0 to 100). Overall, future probabilistic reasoning studies would do well to examine a large sample with a wide range of both self-reported and clinically assessed delusional severity using a similar graded estimates task with decision points and threat ratings, along with affective adaptions of the more methodologically sound Box task.

Conclusions

The current findings indicate that probabilistic reasoning in SZ is closer to optimal probabilistic reasoning (i.e., Bayes inference) than HC after accounting for neurocognition in both neutral and affective contexts. That is, HC underestimate likely events and overestimate unlikely events, a pattern that could be considered "conservative" relative to SZ and Bayes inference. Within the affective context, there were no differences in the estimate deviation from Bayes inference between SZ and HC when estimating the probability of confirmatory threatening evidence coming from an unlikely source, but otherwise SZ estimated closer to Bayes inference than HC for all other conditions of affective evidence coming from an unlikely source. A less "conservative" pattern of probability estimates was related to severe delusional thinking in SZ for affective stimuli (i.e., spies and civilians) but not neutral stimuli (i.e., beads). Thus, a pattern of probabilistic reasoning in SZ that is closer to Bayes inference and less "conservative" than HC may be influenced by affective contexts and related to delusional thinking in SZ.

References

Adams, R. A., Stephan, K. E., Brown, H. R., Frith, C. D., & Friston, K. J. (2013). The computational anatomy of psychosis. *Front Psychiatry, 4*, 47. doi:10.3389/fpsyt.2013.00047

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Andreasen, N. C. (1984). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa.

Balzan, R. P., Delfabbro, P. H., Galletly, C. A., & Woodward, T. S. (2013). Illusory correlations and control across the psychosis continuum: the contribution of hypersalient evidence-hypothesis matches. *J Nerv Ment Dis, 201*(4), 319-327. doi:10.1097/NMD.0b013e318288e229

Batty, R. A., Francis, A., Thomas, N., Hopwood, M., Ponsford, J., & Rossell, S. L. (2016). Who "jumps to conclusions"? A comprehensive assessment of probabilistic reasoning in psychosis following traumatic brain injury (PFTBI), and comparison with TBI, schizophrenia, and nonclinical controls. *Cogn Neuropsychiatry, 21*(1), 32-44. doi:10.1080/13546805.2015.1127221

Bayes, T. (1763). An essay towards solving a problem in the doctrine of chances. *Philosophical Transactions, 53*, 370-418.

Blackwood, N. J., Howard, R. J., Bentall, R. P., & Murray, R. M. (2001). Cognitive neuropsychiatric models of persecutory delusions. *Am J Psychiatry, 158*(4), 527-539. doi:10.1176/appi.ajp.158.4.527

Colbert, S. M., Peters, E., & Garety, P. (2010). Jumping to conclusions and perceptions in early psychosis: relationship with delusional beliefs. *Cogn Neuropsychiatry, 15*(4), 422-440. doi:10.1080/13546800903495684

Demidenko, E. (2013). *Mixed models: Theory and applications with R* (2nd ed.): Wiley.

Dudley, R., Taylor, P., Wickham, S., & Hutton, P. (2016). Psychosis, Delusions and the "Jumping to Conclusions" Reasoning Bias: A Systematic Review and Meta-analysis. *Schizophr Bull, 42*(3), 652-665. doi:10.1093/schbul/sbv150

Dudley, R. E., John, C. H., Young, A. W., & Over, D. E. (1997). The effect of self-referent material on the reasoning of people with delusions. *Br J Clin Psychol, 36 (Pt 4)*, 575-584.

Dudley, R. E. J., & Over, D. E. (2003). People with delusions jump to conclusions: A theoretical account of research findings on the reasoning of people with delusions. *Clinical Psychology & Psychotherapy, 10*(5), 263-274.

Evans, J. B. S. T. (1989). *Biases in human reasoning: Causes and consequences*. Hillsdale, NJ: Erlbaum.

Evans, S. L., Averbeck, B. B., & Furl, N. (2015). Jumping to conclusions in schizophrenia. *Neuropsychiatr Dis Treat, 11*, 1615-1624. doi:10.2147/NDT.S56870

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version, Administration Booklet*: American Psychiatric Press.

Fowler, D., Garety, P., & Kuipers, E. (1995). *Cognitive Behaviour Therapy for Psychosis: Theory and Practice*: Wiley.

Freeman, D. (2007). Suspicious minds: the psychology of persecutory delusions. *Clin Psychol Rev, 27*(4), 425-457. doi:10.1016/j.cpr.2006.10.004

Freeman, D., Garety, P. A., Kuipers, E., Fowler, D., & Bebbington, P. E. (2002). A cognitive model of persecutory delusions. *British Journal of Clinical Psychology, 41*, 331-347.

Freeman, D., Waite, F., Emsley, R., Kingdon, D., Davies, L., Fitzpatrick, R., & Dunn, G. (2016). The efficacy of a new translational treatment for persecutory delusions: study protocol for a randomised controlled trial (The Feeling Safe Study). *Trials, 17*(1), 134. doi:10.1186/s13063-016-1245-0

Garety, P., Joyce, E., Jolley, S., Emsley, R., Waller, H., Kuipers, E., . . . Freeman, D. (2013). Neuropsychological functioning and jumping to conclusions in delusions. *Schizophr Res, 150*(2-3), 570-574. doi:10.1016/j.schres.2013.08.035

Garety, P. A., & Freeman, D. (1999). Cognitive approaches to delusions: a critical review of theories and evidence. *Br J Clin Psychol, 38 (Pt 2)*, 113-154.

Garety, P. A., Hemsley, D. R., & Wessely, S. (1991). Reasoning in deluded schizophrenic and paranoid patients. Biases in performance on a probabilistic inference task. *J Nerv Ment Dis, 179*(4), 194-201.

Green, M. J., & Phillips, M. L. (2004). Social threat perception and the evolution of paranoia. *Neurosci Biobehav Rev, 28*(3), 333-342. doi:10.1016/j.neubiorev.2004.03.006

Hemsley, D. R., & Garety, P. A. (1986). The formation of maintenance of delusions: a Bayesian analysis. *Br J Psychiatry, 149*, 51-56.

Huq, S. F., Garety, P. A., & Hemsley, D. R. (1988). Probabilistic judgements in deluded and non-deluded subjects. *Q J Exp Psychol A, 40*(4), 801-812.

Keefe, R. (1999) Brief Assessment of Cognition in Schizophrenia (BACS). Duke University Medical Center.

Langdon, R., Ward, P. B., & Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. *Schizophr Bull, 36*(2), 321-330. doi:10.1093/schbul/sbn069

Laplace, P. S. (1902). A philosophical essay on probabilities. New York, NY: John Wiley & Sons.

Martinez, A. M., & Benavente, R. (1998). The AR face database. from Report #24

Menon, M., Pomarol-Clotet, E., McKenna, P. J., & McCarthy, R. A. (2006). Probabilistic reasoning in schizophrenia: a comparison of the performance of deluded and nondeluded schizophrenic patients and exploration of possible cognitive underpinnings. *Cogn Neuropsychiatry, 11*(6), 521-536. doi:10.1080/13546800544000046

Moritz, S., Goritz, A. S., Balzan, R. P., Gaweda, L., Kulagin, S. C., & Andreou, C. (2017). A new paradigm to measure probabilistic reasoning and a possible answer to the question why psychosis-prone individuals jump to conclusions. *J Abnorm Psychol, 126*(4), 406-415. doi:10.1037/abn0000262

Moritz, S., & Woodward, T. S. (2004). Plausibility judgment in schizophrenic patients: Evidence for a liberal acceptance bias. *German Journal of PsychIatry, 7*, 66-74.

Moritz, S., & Woodward, T. S. (2005). Jumping to conclusions in delusional and non-delusional schizophrenic patients. *Br J Clin Psychol, 44*(Pt 2), 193-207. doi:10.1348/014466505x35678

Moritz, S., Woodward, T. S., & Lambert, M. (2007). Under what circumstances do patients with schizophrenia jump to conclusions? A liberal acceptance account. *Br J Clin Psychol, 46*(Pt 2), 127-137. doi:10.1348/014466506X129862

Morrison, P. D., & Murray, R. M. (2009). From real-world events to psychosis: the emerging neuropharmacology of delusions. *Schizophr Bull, 35*(4), 668-674. doi:10.1093/schbul/sbp049

Phillips, L. D., & Edwards, W. (1966). Conservatism in a simple probability inference task. *Journal of Experimental Psychology, 72*(3), 346-354. doi:10.1037/h0023653

Rainie, L., & Madden, M. (2015). *Americans' views on government surveillance programs*. Retrieved from

Roa Romero, Y., Keil, J., Balz, J., Gallinat, J., & Senkowski, D. (2016). Reduced frontal theta oscillations indicate altered crossmodal prediction error processing in schizophrenia. *J Neurophysiol, 116*(3), 1396-1407. doi:10.1152/jn.00096.2016

Ross, R. M., McKay, R., Coltheart, M., & Langdon, R. (2015). Jumping to Conclusions About the Beads Task? A Meta-analysis of Delusional Ideation and Data-Gathering. *Schizophr Bull, 41*(5), 1183-1191. doi:10.1093/schbul/sbu187

Speechley, W. (2010). The contribution of hypersalience to the “jumping to conclusions” bias associated with delusions in schizophrenia. *Journal of Psychiatry and Neuroscience, 35*(1), 7-17. doi:10.1503/jpn.090025

Tversky, A., & Kahneman, D. (1974). Judgment under uncertainty: Heuristics and baises. *Science, 185*(4157), 1124-1131.

Tversky, A., & Kahneman, D. (1983). Extensional versus intuitive reasoning: The conjunction fallacy in probability judgment. *Psychological Review, 90*(4), 293-315.

Warman, D. M., Martin, J. M., & Lysaker, P. (2013). Jumping to conclusions and delusions: the impact of discussion of the bias on the bias. *Schizophr Res, 150*(2-3), 575-579. doi:10.1016/j.schres.2013.09.003

WHO. (2004). *Global Burden of Disease*: World Health Organization.

Table 4.1: Demographic and clinical characteristics of HC and SZ participants

	Scale Range	HC (*n*=24)	SZ (*n*=25)	*t*/chi-square
Age (years)		43.0 (15.0)	43.7 (13.7)	0.18
Sex (Male/Female)		12/12	12/13	0.02
Level of education	1-8	6.3 (1.6)	5.1 (1.6)	-2.58*
BACS		0.0 (1.0)	-0.6 (0.8)	-2.22*
BDI-IA	0-63	0.8 (1.6)	8.8 (6.4)	5.98***
STAI-S	20-80	26.2 (4.1)	37.6 (10.2)	5.07***
SAPS Total	0-20	--	5.1 (3.4)	
SAPS Delusions	0-5	--	2.0 (1.3)	
SANS	0-20	--	5.6 (2.8)	
Daily CPZ equivalent (*n*=16)		--	527.8 (834.8)	
Duration of Illness (years)		--	27.6 (13.5)	
Hospitalizations		--	5.3 (6.0)	

Note. SZ = schizophrenia. HC = healthy control. Level of education is comprised of eight levels: 1) grade 6 or less, 2) grade 12 but did not graduate, 3) high school diploma or equivalent, 4) part college, 5) associate’s degree, 6) bachelor’s degree, 7) part graduate or professional school, 8) graduate or professional school degree. BACS = Brief Assessment of Cognition in Schizophrenia *z*-score. BDI-IA = revised version of the Beck Depression Inventory. STAI-S = state subscale of the State-Trait Anxiety Inventory. SAPS Total = Scale for the Assessment of Positive Symptoms total score. SAPS Delusions = delusions subscale of the Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. CPZ = chlorpromazine (dosage unavailable for eight patients). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 4.2: ANCOVA and LMM for Estimate Deviation from Bayes Calculation for the Neutral and Affective Consistently-Confirmatory Sequence

	A Neutral Consistently-Confirmatory Sequence[a]		B Affective Consistently-Confirmatory Sequence[b]	
	Likely Jar	Unlikely Jar	Likely Building	Unlikely Building[c]
Tests of Fixed Effects				
Intercept	*F*(1, 46.0) = 12.25**	*F*(1, 46.0) = 23.9***	*F*(1, 46.6) = 8.37**	*F*(1, 46.0) = 15.18***
Group (HC, SZ)	*F*(1, 46.0) = 8.87**	*F*(1, 46.0) = 9.89**	*F*(1, 46.0) = 15.33***	*F*(1, 46.0) = 11.54**
BACS	*F*(1, 46.0) = 10.58**	*F*(1, 46.0) = 17.73***	*F*(1, 46.0) = 24.66***	*F*(1, 46.0) = 25.53***
Stimuli (Spy, Civilian)	--	--	*F*(1, 48.0) = 2.25	*F*(1, 48.0) = 1.42
Estimates of Fixed Effects[d]	β *(s.e.)*	β *(s.e.)*	β *(s.e.)*	β *(s.e.)*
Intercept	-0.85 (2.39)	2.96 (2.49)	0.81 (2.36)	1.44 (2.56)
HC	-9.71 (3.26)**	10.67 (3.39)**	-11.91 (3.04)***	11.61 (3.42)**
BACS	5.73 (1.76)**	-7.72 (1.83)***	8.15 (1.64)***	9.33 (1.85)***
Spy	--	--	1.24 (0.83)	-1.17 (0.98)
Model Information Criteria				
-2 REML log-likelihood	359.9	363.6	662.3	689.2
AIC	361.9	365.6	668.3	693.2
BIC	363.7	367.4	675.9	698.2

a. Analysis of Covariance (ANCOVA)
b. Linear Mixed Model (LMM)
c. Repeated effects (evidence type and stimuli type) removed due to convergence error
d. Redundant parameters omitted

* *p* < .05 ** *p* < .01 *** *p* < .001

Table 4.3: LMM for Estimate Deviation from Bayes Calculation for the Neutral and Affective Mixed Sequence

		Neutral Mixed Sequence[a]			Affective Mixed Sequence	
	A	Likely Jar	Unlikely Jar	B	Likely Building	Unlikely Building
Tests of Fixed Effects						
Intercept		*F*(1, 44.9) = 7.75**	*F*(1, 45.0) = 15.71***		*F*(1, 53.0) = 8.08**	*F*(1, 50.6) = 12.66**
Group (HC, SZ)		*F*(1, 44.9) = 7.04*	*F*(1, 44.9) = 6.43*		*F*(1, 45.7) = 11.2**	*F*(1, 50.6) = 8.11**
BACS		*F*(1, 45.2) = 11.74**	*F*(1, 45.0) = 22.94***		*F*(1, 52.7) = 13.9***	*F*(1, 50.3) = 17.9***
Evidence (Confirmatory, Disconfirmatory)		*F*(1, 46.4) = 2.94	*F*(1, 44.4) = 0.09		*F*(1, 98.9) = 3.38	*F*(1, 99.7) = 0.25
Evidence x BACS		--	*F*(1, 44.6) = 8.97**		*F*(1, 97.0) = 6.21*	*F*(1, 87.7) = 10.09**
Stimuli (Spy, Civilian)		--	--		*F*(1, 54.9) = 2.22	*F*(1, 96.3) = 0.35
Evidence x Stimuli x Group		--	--		--	*F*(1, 59.5) = 2.57*
Estimates of Fixed Effect[b]		β *(s.e.)*	β *(s.e.)*		β *(s.e.)*	β *(s.e.)*
Intercept		-1.46 (2.6)	2.64 (2.6)		-0.93 (2.65)	-0.04 (3.08)
HC		-9.0 (3.39)*	8.72 (3.44)*		-10.98 (3.28)**	10.99 (4.22)*
BACS		6.3 (1.84)**	-10.85 (1.98)***		8.38 (2.09)***	-9.64 (2.07)***
Confirmatory		2.48 (1.44)	-0.37 (1.26)		2.14 (1.17)	1.42 (2.06)
Confirmatory, BACS		--	3.91 (1.3)**		-3.04 (1.22)*	3.16 (1.0)**
Spy		--	--		1.0 (0.67)	1.96 (2.37)
Spy, Confirmatory, HC		--	--		--	-5.07 (4.36)
Spy, Confirmatory, SZ		--	--		--	-1.57 (2.59)
Spy, Disconfirmatory, HC		--	--		--	0.41 (3.36)
Civilian, Confirmatory, HC		--	--		--	-0.57 (2.88)
Model Information Criteria						
-2 REML log-likelihood		717.6	690.4		1375.6	1299.2
AIC		721.6	694.4		1385.6	1309.2
BIC		726.7	699.5		1401.8	1325.1

a. Sequence was analyzed without repeated effects due to smaller model information criteria values for the model without repeated effects compared with the model with repeated effects.

b. Redundant parameters omitted.

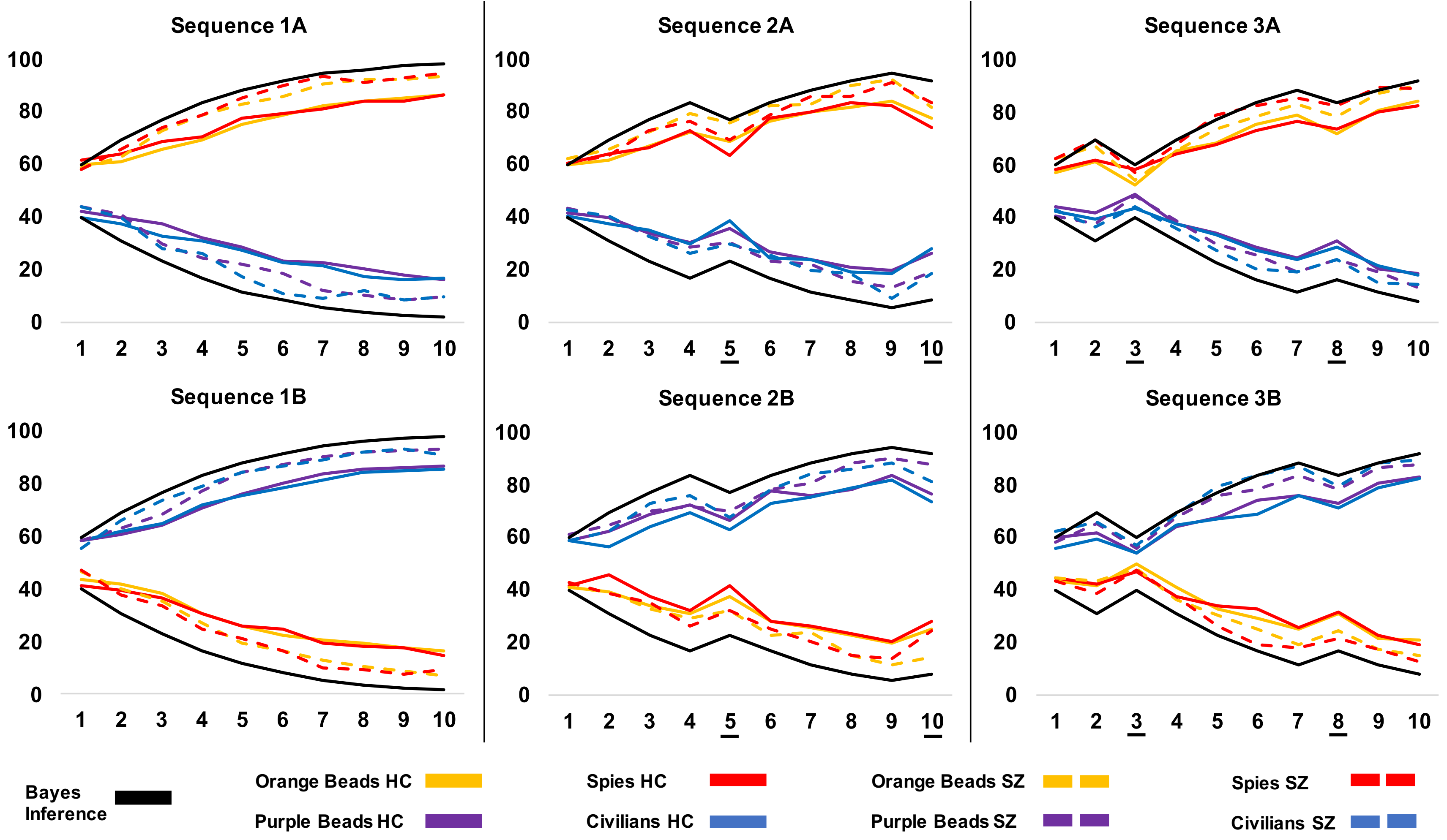
* $p < .05$ ** $p < .01$ *** $p < .001$

Supplemental Table 4.1: Pearson Correlations Between SAPS Delusions and Estimate Deviations for the Neutral and Affective Consistently-Confirmatory Sequence

SZ (*n* = 25)	SAPS Delusions
Sequence 1 Likely Jar	0.23
Sequence 1 Unlikely Jar	-0.19
Sequence 1 Likely Building	0.24
Sequence 1 Unlikely Building	-0.17

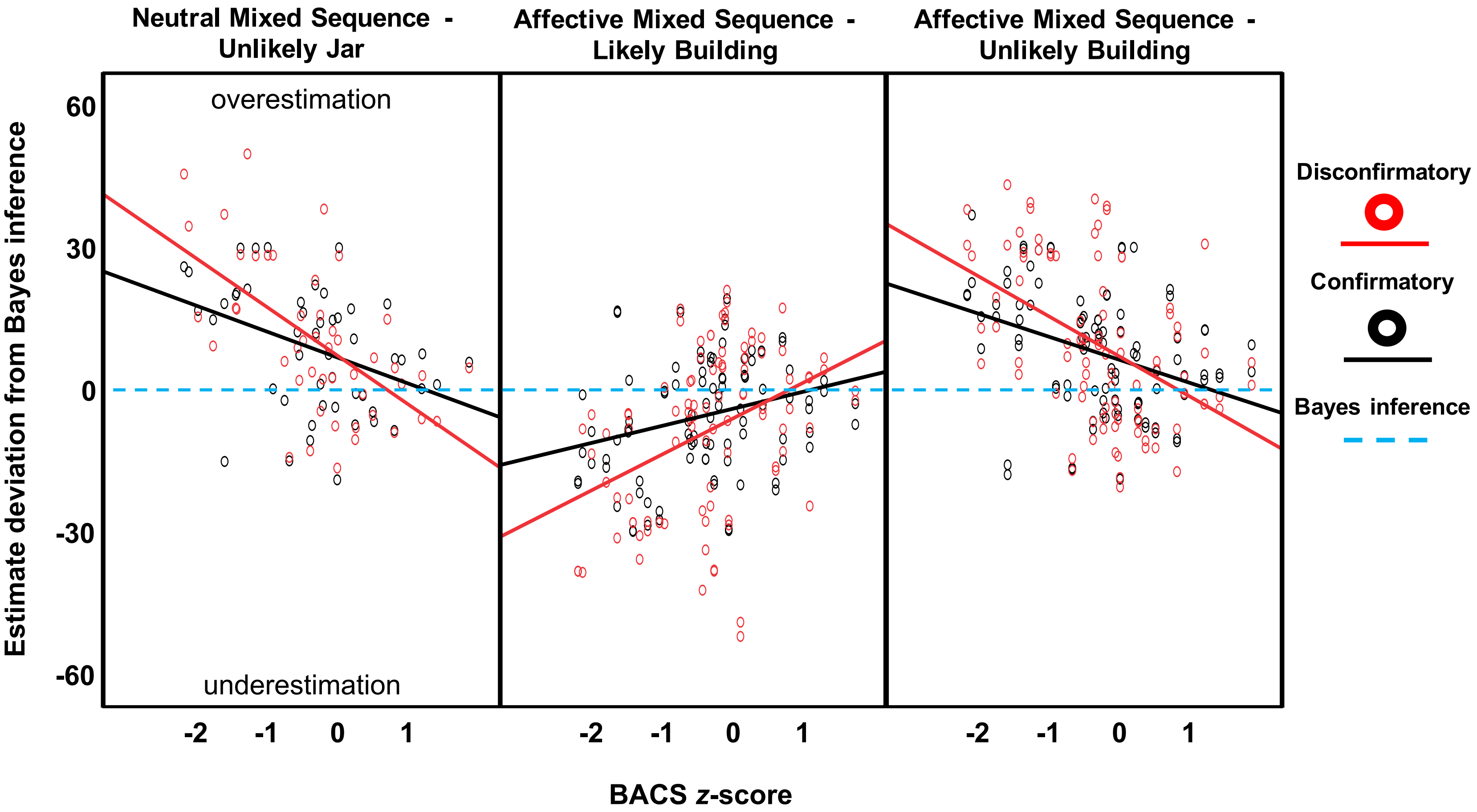
Note. SZ = schizophrenia. HC = healthy control. SAPS delusions = Delusions subscale of the Scale for the Assessment of Positive Symptoms. Analyses were repeated with Spearman’s rank order correlation and found to be nearly identical.

Figure 4.1



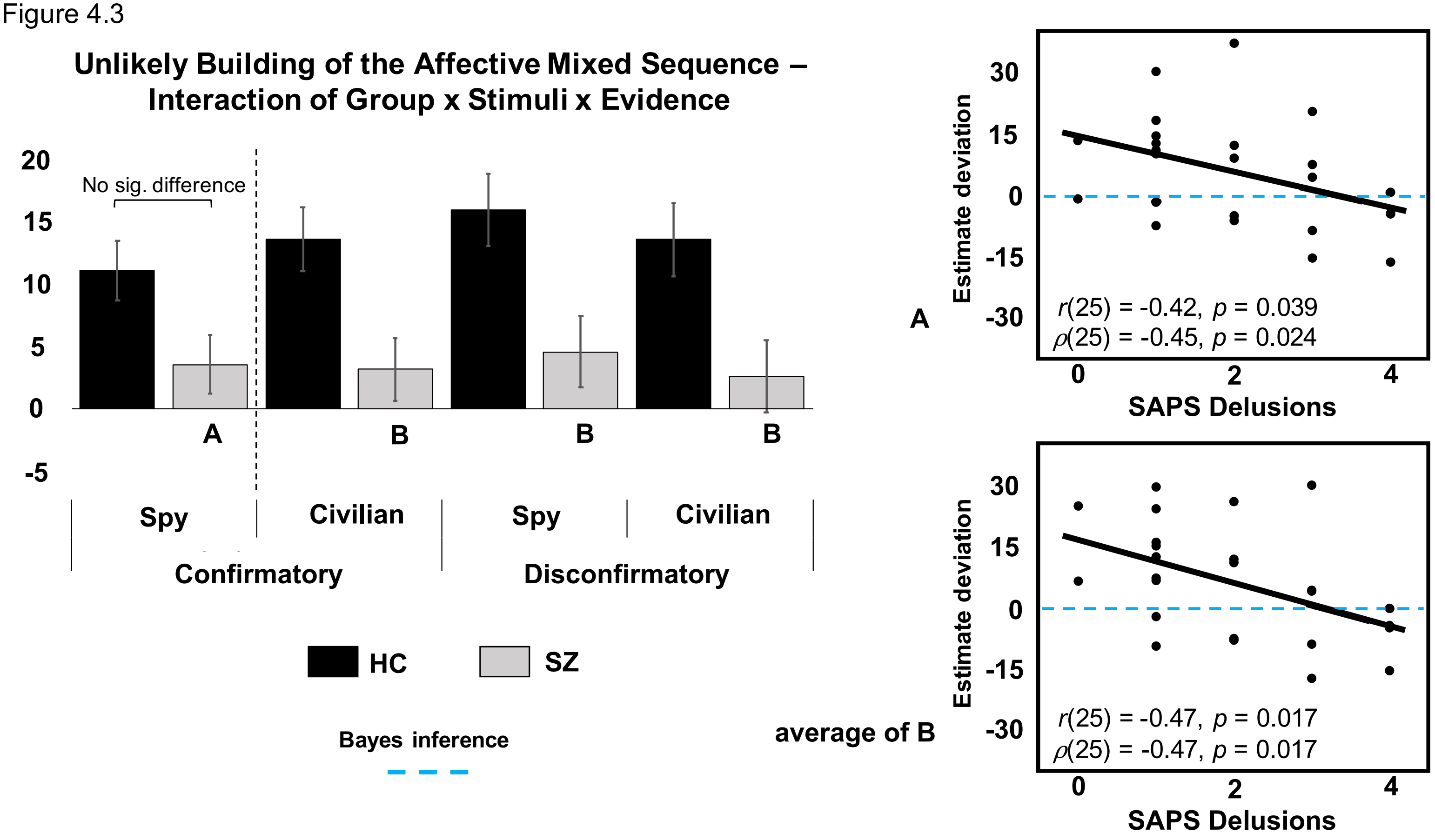
Note: Raw probability estimates for each sequence and group. HC = healthy control. SZ = schizophrenia. Sequence 1A reversed the likely jar compared with Sequence 1B (e.g., mainly-orange jar is likely in Sequence 1A and mainly-purple jar is likely in Sequence 1B). Sequences 1A and 1B were averaged together and referred to as the neutral or affective Consistently-Confirmatory Sequence. Disconfirmatory evidence within sequences 2A, 2B, 3A, and 3B is designated by the stimulus number being underlined. Sequences 2A, 2B, 3A, and 3B are referred to as the neutral or affective Mixed Sequence.

Figure 4.2



Note: Two-way interaction between evidence type and neurocognition for estimate deviation across all participants. Evidence type = confirmatory or disconfirmatory. Estimate deviation is included for: 1) the unlikely jar of the neutral Mixed Sequence, 2) the likely building of the affective Mixed Sequence, and 3) the unlikely building of the affective Mixed Sequence. BACS = Brief Assessment of Cognition in Schizophrenia. Estimate deviation was calculated by subtracting the participant's probability estimates from Bayes calculation.

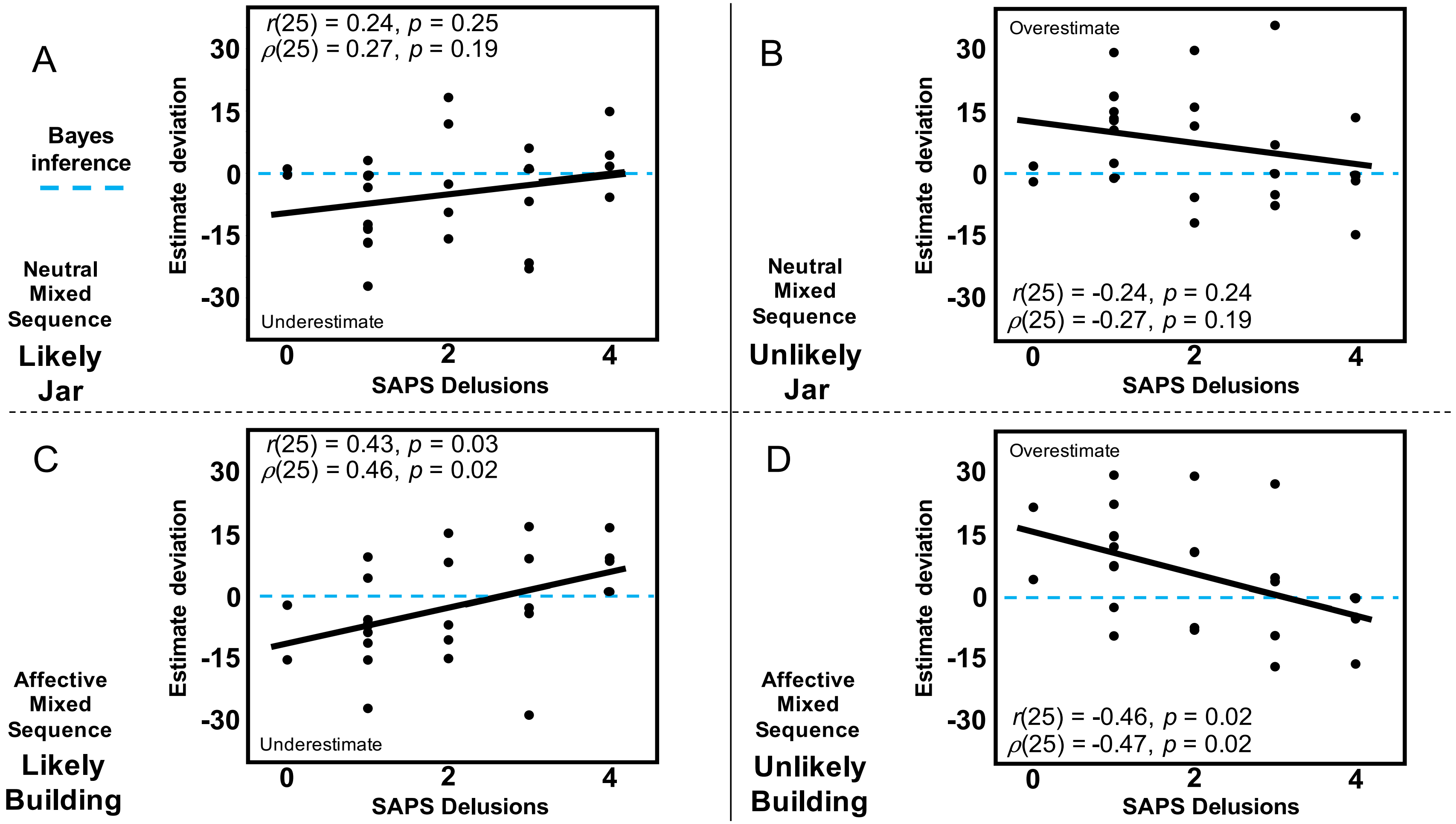
Figure 4.3



Unlikely Building of the Affective Mixed Sequence – Interaction of Group x Stimuli x Evidence

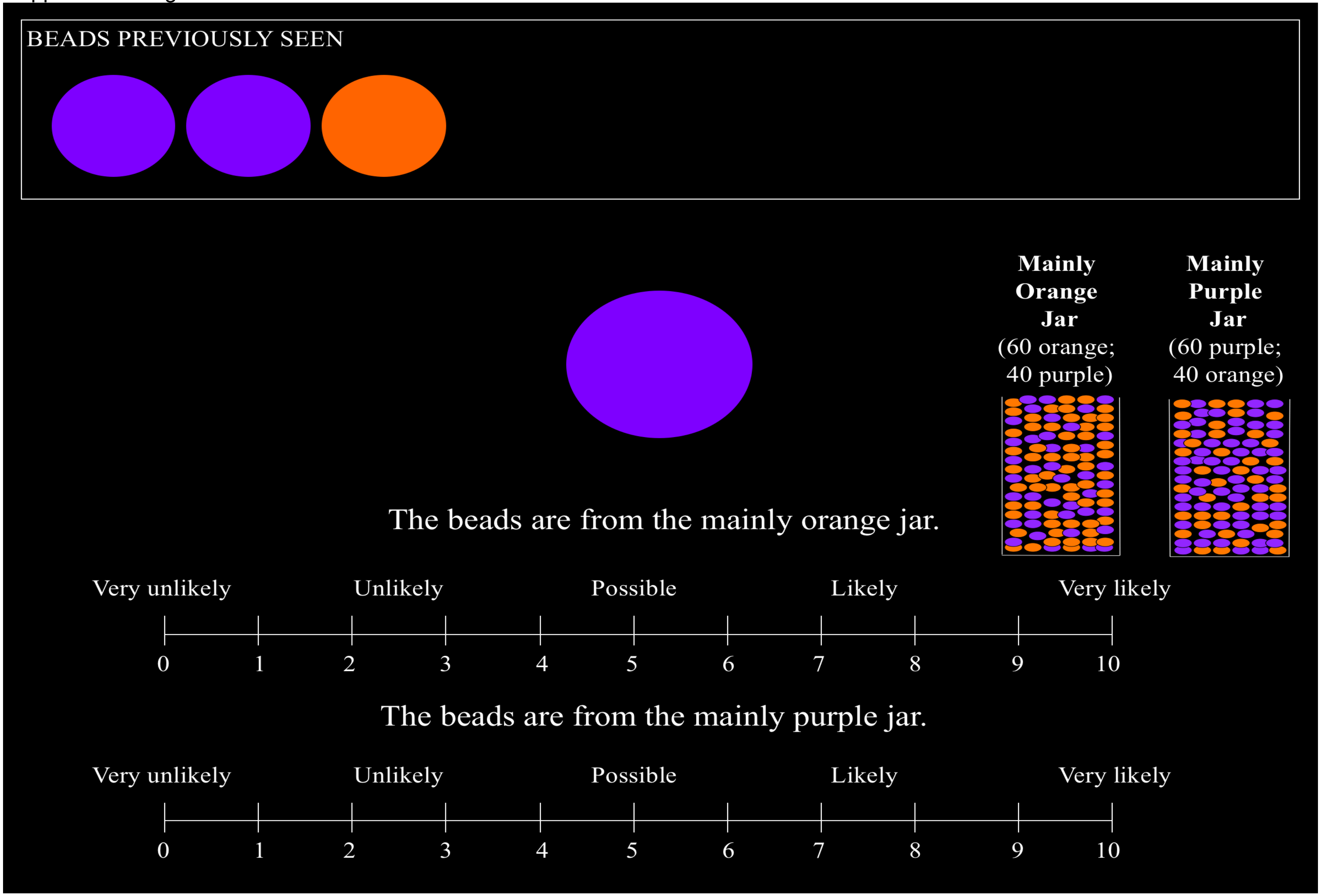
Note: Group differences in estimated means for the group by stimuli by evidence type interaction. The bar graph shows the estimated marginal means of the three-way interaction between group, stimuli, and evidence type for the unlikely building in the affective Mixed Sequence determined with a linear mixed model. Bars indicate standard error. Estimate deviation from Bayes inference was calculated by subtracting the participant's probability estimate from Bayes calculation. For the unlikely source, estimate deviation with a higher value indicates a more conservative approach to probabilistic reasoning relative to Bayes inference. Contrast interaction comparing confirmatory spies and an average of confirmatory civilians, disconfirmatory spies, and disconfirmatory civilians between the groups showed that SZ were significantly closer to Bayes inference and less conservative than HC for all combinations of stimuli and evidence type except for confirmatory spies. The scatterplots on the right show the Pearson and Spearman's rank order correlations between SAPS Delusions and estimate deviation for confirmatory spies (gray bar labeled A; top scatterplot) and estimate deviation for the average of the three gray bars labeled B (confirmatory civilians, disconfirmatory spies, and disconfirmatory civilians).

Figure 4.4



Note: Pearson and Spearman’s rank order correlations between probabilistic reasoning and delusional thinking in people with schizophrenia. SAPS Delusions = Delusions subscale of the Scale for the Assessment of Positive Symptoms. Estimate deviation from Bayes inference was calculated by subtracting the participant’s probability estimate from Bayes calculation. For the likely source, estimate deviation with a lower value indicates a more conservative approach to probabilistic reasoning relative to Bayes inference. For the unlikely source, estimate deviation with a higher value indicates a more conservative approach to probabilistic reasoning relative to Bayes inference. Significant Pearson and Spearman’s rank order correlations between SAPS Delusions and the estimate deviation for the likely and unlikely jars and then likely and unlikely buildings for participants with schizophrenia are provided in Parts A, B, C, and D, respectively.

Supplemental Figure 4.1



BEADS PREVIOUSLY SEEN

Mainly Orange Jar
(60 orange; 40 purple)

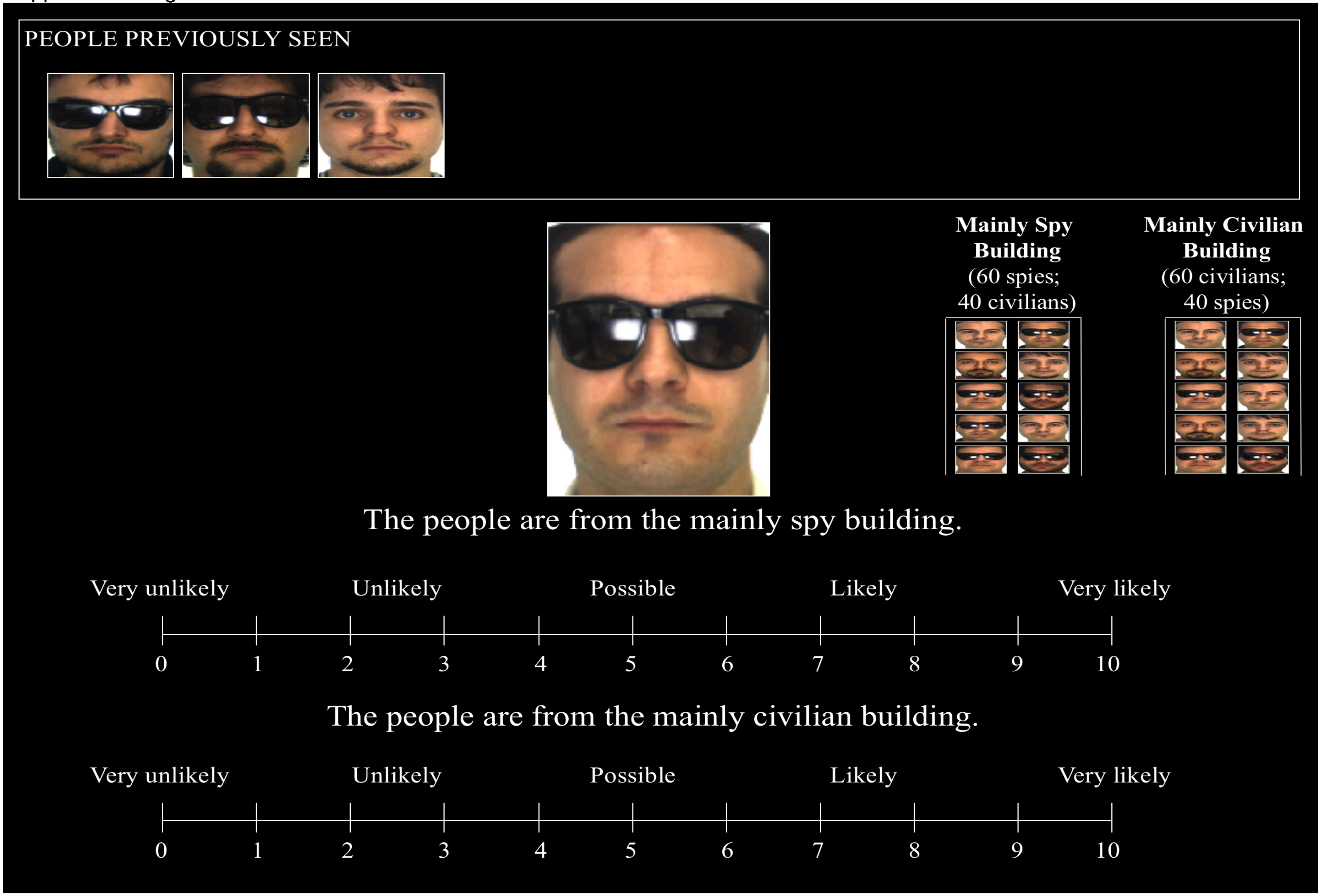
Mainly Purple Jar
(60 purple; 40 orange)

The beads are from the mainly orange jar.

The beads are from the mainly purple jar.

Note: Example of the neutral version of the graded estimates task.

Supplemental Figure 4.2

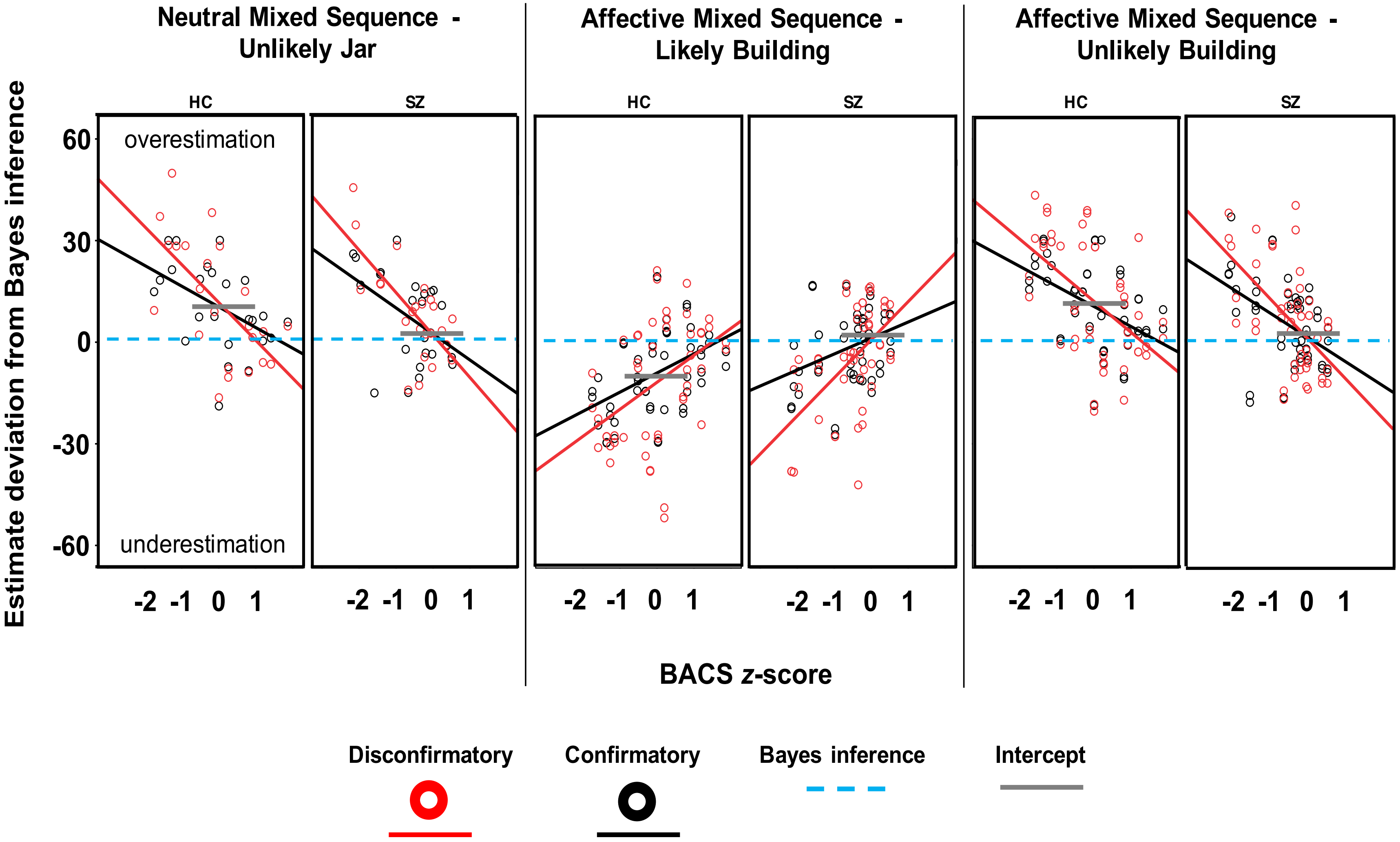


The people are from the mainly spy building.

The people are from the mainly civilian building.

Note: Example of the affective version of the graded estimates task.

Supplemental Figure 4.3



Note: Illustration of the intercept group difference in estimate deviation for the two-way interaction between neurocognition and evidence type. Specifically, linear mixed model two-way interaction between evidence type (confirmatory or disconfirmatory) and neurocognition (BACS *z*-score) plotted for SZ and HC estimate deviations to show the intercept difference between the groups. HC = healthy control. SZ = schizophrenia. BACS = Brief Assessment of Cognition in Schizophrenia.

CHAPTER 5

Summary and Conclusions

This dissertation aimed to further our understanding of cognitive and affective processes linked to distress and poor functional outcomes in schizophrenia. The use of self-report measures and behavioral tasks allowed us to examine the relationship between: 1) emotional experience and social functioning in psychotic and affective disorders, 2) paranoia and sound localization in schizophrenia, and 3) delusions and affective probabilistic reasoning in schizophrenia. The methods and findings of each study are summarized below.

Study 1

Participant data was aggregated from multiple studies (N = 1,118) with similar self-report measures of emotional experience and social functioning to determine the relationship these two constructs while accounting for "traditional" predictors of functioning that include general cognition or intelligence, social cognition, positive and negative symptoms, and mania. Measures of negative and positive affect included the Beck Depression Inventory, State-Trait Anxiety Inventory, Psychological Stress Index, Differential Emotions Scale, Positive and Negative Affect Scale, and Mood and Anxiety Symptom Questionnaire. Social functioning was assessed with the Social Adjustment Scale – Self Report). Neurocognition was assessed with the Brief Assessment of Cognition in Schizophrenia. Social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test), positive symptoms (Scale for the Assessment of Positive Symptoms), negative symptoms (Scale for the Assessment of Negative Symptoms), and mania (Young Mania Rating Scale) were used. Hierarchical linear regression was used to determine if measures of emotional experience predicted a significant amount of variance in social functioning above and beyond “traditional” predictors of functioning.

Study 2

Participants with schizophrenia (*n* = 20) and matched controls with no history of mental illness (*n* = 22) localized 48 auditory stimuli from the International Affective Digitized Sounds database. The sound localization paradigm consisted of a 360-degree horizontal plane with eight active speakers. The Green at al. Paranoid Thoughts Scale was used to determine level of paranoia, and neurocognition was assessed with the Brief Assessment of Cognition in Schizophrenia. Participants rated the valence and arousal elicited for each sound. Absolute error was calculated in order to obtain an accurate reflection of sound localization performance (i.e., negative values could artificially reduce the amount of total error). A gamma distribution was observed due to relatively strong performance of participants (resulting in a high concentration of accurate performances and a right skew for localization error) and a generalized linear model was used to appropriately examine if sound localization performance was related to individual or standardized ratings of valence and arousal. Pearson and Spearman’s rank order correlations were used to determine the relationship between paranoia and mean absolute error, along with partial correlation between paranoia and mean absolute error while accounting for neurocognition.

Study 3

Participants with schizophrenia (*n* = 27) and matched controls with no history of mental illness (*n* = 24) completed a neutral and affective version of a probabilistic reasoning task. Participants provided probability estimates of how likely a sequences of color beads or affective stimuli (i.e., threatening spies or non-threatening civilians) was coming from a likely and unlikely source. Each sequence included ten pieces of evidence comprised of all confirmatory evidence or a mix of confirmatory and disconfirmatory evidence. Probability estimates were compared against Bayes inference for all analyses, resulting in an estimate deviation score for the likely and unlikely source according to evidence type (confirmatory or disconfirmatory) and stimuli type (threatening or non-threatening) for the affective version only. Analysis of covariance and linear mixed models were used to determine group differences in estimate deviation, along with additional main effects of evidence or stimuli type and any possible interactions between main effects. Delusional severity in SZ was assessed with the delusions subscale of the Scale for the Assessment of Positive Symptoms. The relationship between delusions and estimate deviation was determined with Pearson and Spearman's rank order correlations.

Taken together, this dissertation research showed that heightened negative- and reduced positive emotional experience is related to social functioning impairment in psychotic disorders, affective disorders, psychiatrically healthy individuals, and an online crowdsourcing sample representative of the general population above and beyond "traditional" predictors of functioning in serious mental illnesses that include general cognition or intelligence, social cognition, positive or negative symptoms, and mania. These findings suggest that emotional experience is associated with social functioning along a continuum of psychiatrically healthy individuals to people with a serious mental illness. This is consistent with previous research that suggests a relationship between heightened negative affect, reduced positive affect, and social functioning in schizophrenia, bipolar disorder, and major depression (Havermans, Nicolson, Berkhof, & deVries, 2010; Hofmann & Meyer, 2006; Kring & Moran, 2008; Myin-Germeys et al., 2003; Oorschot et al., 2013). In addition, people with schizophrenia had difficulty localizing natural sounds that occur in the environment (e.g., someone yelling) compared with those with no history of mental illness, similar to previous reports of localization impairment of laboratory stimuli (e.g., clicks or tones) in people with schizophrenia (Balogh, Schuck, & Leventhal, 1979; Perrin et al., 2010). For those with schizophrenia, this impairment was related to reduced levels of paranoia. Sound localization was also influenced by standardized but not individual ratings of valence and arousal among all participants, with the influence of arousal on sound localization deficits increasing with more unpleasant sounds. Thus, sound localization deficits are characteristic of schizophrenia, yet within schizophrenia heightened levels of paranoia associated with improved sound localization even when accounting for neurocognition. Finally, probabilistic reasoning of confirmatory and disconfirmatory evidence coming from a likely and unlikely source during neural and affective contexts is closer to Bayes inference for people with schizophrenia compared with those without a history of mental illness. That is, healthy individuals demonstrated of conservative pattern of probabilistic reasoning by underestimating likely events and overestimating unlikely events relative to people with schizophrenia and also Bayes inference. However, within the affective context, healthy individuals demonstrated probabilistic reasoning similar to people with schizophrenia for threatening confirmatory evidence only. In addition, less conservative probability estimates were related to more severe delusional thinking in people with schizophrenia within the affective context only. While the finding of less conservative probabilistic reasoning in people with schizophrenia compared with healthy individuals is consistent with previous reports (Garety, Hemsley, & Wessely, 1991; Langdon, Ward, & Coltheart, 2010; Speechley, 2010), the current findings suggest that probabilistic reasoning is influenced by affective contexts and that a less conservative pattern of probabilistic reasoning could play a role in delusional thinking in people with schizophrenia.

The findings of this dissertation may help to inform the cognitive model that is the basis for cognitive-behavioral therapy for psychosis (CBTp). According to this model, a cycle of biased processing of events/stimuli contribute to distorted interpretations of these experiences and the development of maladaptive emotional and behavioral responses (Beck, 1963, 2005). Despite evidence for the improved outcomes post CBTp treatment (Kane et al., 2016), a better understanding of this model could lead to increased effectiveness. The observed relationship between social functioning deficits and heightened negative emotions, and also reduced positive emotions, in Study 1 lends support for a strong association between maladaptive emotions and behaviors. In addition, the transdiagnostic approach used in Study 1 suggests that a unified treatment protocol targeting emotional experience may be appropriate for psychotic and affective disorders. While the causal relationship is unknown, it is possible that mundane social interactions are experienced as stressful events that elicit heightened negative affect (Myin-Germeys et al., 2003). The observed deficits in sound localization in people with schizophrenia compared with healthy individuals in Study 2 suggests that people with schizophrenia there may be susceptible to misinterpreting the environment, which could contribute to biased processing of events/stimuli and the development of maladaptive emotions and behaviors purported to arise in the CBTp model. Yet, the relationship between heightened paranoia (which could also promote biased interpretations of events/stimuli), and improved sound localization in people with schizophrenia indicates attentional and sensory resources may be allocated to help compensate for localization deficits. However, further research is needed to elucidate the relationship between paranoia and sound localization, along with the functional impact of sound localization deficits in schizophrenia. The observed probabilistic reasoning style of overestimating likely events and underestimating unlikely events in people with schizophrenia relative to healthy individuals in Study 3 suggests that while people with schizophrenia may estimate probability more accurately, this may not be adaptive, as the relationship between increased delusional severity and a less conservative pattern of probabilistic reasoning in SZ (relative to HC) was observed. Incorporating the findings of this dissertation with the example used in the Introduction, the sound of a neighbor walking through your yard late at night may be hastily misinterpreted (sound localization deficits reported in Study 2 may contribute to this misinterpretation and the neighbor could be walking through a different yard) as a suspicious act due to overestimation of what is considered a likely event and underestimation of unlikely event (person is not acting suspicious), which was reported in Study 3. This perceived threat might lead to the evocation of negative affect that helps to reinforce the belief (e.g., “I feel fear and anxiety so this person is a threat”) and behavioral changes such as avoiding neighbors.

Heightened negative affect (reported in Study 1) and repeated avoidance could result in missed opportunities to challenge this hasty conclusion, and along with a less conservative style of probabilistic reasoning relative healthy individuals, could lead to a false belief or delusion.

To conclude, the results of this dissertation helped to inform cognitive models of psychotic symptoms. By examining emotional experience and social functioning, paranoia and the interpretation of the environment, and affective probabilistic reasoning and delusions in people with schizophrenia, the current findings may help to enhance our understanding of critical psychosocial treatment targets and provide directions for future research and treatment development.

References

Balogh, D. W., Schuck, J. R., & Leventhal, D. B. (1979). A study of schizophrenics' ability to localize the source of a sound. *J Nerv Ment Dis, 167*(8), 484-487.

Beck, A. T. (1963). Thinking and Depression. I. Idiosyncratic Content and Cognitive Distortions. *Arch Gen Psychiatry, 9*, 324-333.

Beck, A. T. (2005). The current state of cognitive therapy: a 40-year retrospective. *Arch Gen Psychiatry, 62*(9), 953-959. doi:10.1001/archpsyc.62.9.953

Garety, P. A., Hemsley, D. R., & Wessely, S. (1991). Reasoning in deluded schizophrenic and paranoid patients. Biases in performance on a probabilistic inference task. *J Nerv Ment Dis, 179*(4), 194-201.

Havermans, R., Nicolson, N. A., Berkhof, J., & deVries, M. W. (2010). Mood reactivity to daily events in patients with remitted bipolar disorder. *Psychiatry Res, 179*(1), 47-52. doi:10.1016/j.psychres.2009.10.020

Hofmann, B. U., & Meyer, T. D. (2006). Mood fluctuations in people putatively at risk for bipolar disorders. *Br J Clin Psychol, 45*(Pt 1), 105-110. doi:10.1348/014466505X35317

Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., . . . Heinssen, R. K. (2016). Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. *American Journal of Psychiatry, 173*(4), 362-372. doi:10.1176/appi.ajp.2015.15050632

Kring, A. M., & Moran, E. K. (2008). Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull, 34*(5), 819-834. doi:10.1093/schbul/sbn071

Langdon, R., Ward, P. B., & Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. *Schizophr Bull, 36*(2), 321-330. doi:10.1093/schbul/sbn069

Myin-Germeys, I., Peeters, F., Havermans, R., Nicolson, N. A., DeVries, M. W., Delespaul, P., & Van Os, J. (2003). Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatr Scand, 107*(2), 124-131.

Oorschot, M., Lataster, T., Thewissen, V., Lardinois, M., Wichers, M., van Os, J., . . . Myin-Germeys, I. (2013). Emotional experience in negative symptoms of schizophrenia--no evidence for a generalized hedonic deficit. *Schizophr Bull, 39*(1), 217-225. doi:10.1093/schbul/sbr137

Perrin, M. A., Butler, P. D., DiCostanzo, J., Forchelli, G., Silipo, G., & Javitt, D. C. (2010). Spatial localization deficits and auditory cortical dysfunction in schizophrenia. *Schizophr Res, 124*(1-3), 161-168. doi:10.1016/j.schres.2010.06.004

Speechley, W. (2010). The contribution of hypersalience to the “jumping to conclusions” bias associated with delusions in schizophrenia. *Journal of Psychiatry and Neuroscience, 35*(1), 7-17. doi:10.1503/jpn.090025